Medicines Adverse Reactions Committee

Meeting date	11 June 2020	Agenda item	3.2.3
Title	**Use of oral sedating antihistamines in children for sedation**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredients brompheniramine, chlorphenamine, cyclizine, dexchlorpheniramine, diphenhydramine, doxylamine, meclozine, promethazine Note: These active ingredients are contained either alone or in combination with other active ingredients. Only those contained in products with consent given and formulated for oral use are listed.			
PHARMAC funding	chlorphenamine, cyclizine, dexchlorpheniramine and promethazine have products funded in the pharmaceutical schedule		
Previous MARC meetings	Use of dexchlorpheniramine and other sedating antihistamines in children (June 2016)		
Prescriber Update	Changes regarding the use of sedating antihistamines (September 2018) Children and sedating antihistamines (March 2013)		
Classification	Varies from pharmacy only to prescription (www.medsafe.govt.nz/profs/class/classintro.asp)		
Usage data	Difficult to obtain as some products are available over-the-counter (OTC)		
Advice sought	**The Committee is asked to advise on the following:** • Should the use of oral sedating antihistamines in children for sedation (currently from the age of 2 years) be increased to an older age? If so, what age should this be? • Does this require further communication other than MARC's Remarks in *Prescriber Update*?		

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1 PURPOSE

Oral sedating antihistamines are used for a range of conditions in both adults and children. Although the use of oral sedating antihistamines for insomnia is contraindicated for children under 12 years old, there are products available for use in children from the age of 2 years for sedation. Therefore, this paper focuses on the use of these medicines in children aged 2 to <12 years for sedation.

2 BACKGROUND

Insomnia is not the same as sedation, although sedative medicines may be used to treat insomnia.

2.1 Sleep [2]

Sleep is a rapidly reversible state of reduced responsiveness, motor activity and metabolism. Sleep is analysed in 30-second epochs, each of which is categorised as rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep:

- NREM sleep is divided into three stages: N1, N2 and N3. Most of the total sleep time in adults is spent in NREM sleep.
- REM sleep is characterised by three main features: a low voltage mixed frequency EEG pattern, rapid eye movements and voluntary muscle atonia, except the extraocular muscles and diaphragm. Although a minority of sleep time is spent in REM sleep, it has important roles in physiological homeostasis and cognition.

Sleep stages occur in cycles lasting 90 to 120 minutes each. Four to five cycles occur during a typical night of sleep. Shifting of stages occurs over the course of the night, usually with increased percentage of NREM sleep in the first half of the night (particularly stage N3) and increased percentage of REM sleep in the second half of the night. Changes in typical sleep architecture may be representative of sleep disorders, but there are many other causes.

The true purpose of sleep is not well understood. Empirical and experimental data support a variety of potential functions including energy conservation, restoration and clearance of metabolites, and promotion of brain plasticity.

2.1.1 Sleep in children and adolescents [3]

In normal older children and adolescents, sleep is characterised by:

- onset via NREM sleep
- NREM sleep occupying about 75% of total sleep time
- REM and NREM sleep alternating throughout the night with a period of 90 to 100 minutes, and a progressive lengthening of the duration of REM sleep periods in the final third of the night.

Sleep in adolescents is further characterised by:

- decrease in slow-wave sleep beginning in puberty and continuing into adulthood
- physiologic shift in sleep onset to a later time
- increasing irregularity of sleep-wake patterns (primarily discrepancies between weeknights and weekend sleep patterns)
- decrease in average sleep duration despite relatively stable sleep requirement of about nine hours.

2.1.2 Histamine's effect on sleep-wake cycle [4]

Histamine containing neurons are mainly located in the tuberomammillary nucleus (TMN) and adjacent areas within the posterior hypothalamus. The posterior hypothalamus is thought to have a role in the regulation of wakefulness since the early 20th century. Histaminergic neurons send strong projections especially to the wakefulness promoting regions including the orexin rich perifornical hypothalamus and the cholinergic rich basal forebrain. The discharge activity of histaminergic neurons peaks during the state of high vigilance and

ceases during NREM and REM sleep. Histamine release parallels histaminergic discharge (highest during wakefulness and lowest during sleep). Pharmacological evidence suggests the H1 and H3 receptor (but not H2 receptors) are key mediators of histaminergic action on wakefulness.

First generation antihistamines can penetrate the blood brain barrier and cause drowsiness and sedation. Several of these antihistamines, including those from the phenothiazine class (eg, promethazine) and diphenhydramine, have been studied.

Risberg et al 1975 found that administration of promethazine (50 mg, 100 mg, 200 mg) at bedtime in 10 healthy volunteers induced a dose dependent reduction in REM sleep followed by a significant increase in REM sleep on the post-drug "withdrawal" night [5]. They also found administration of 100 mg promethazine at bedtime for 9 days induced a profound suppression of REM sleep that peaked on day-1 and returned to placebo values by day-9, followed by REM rebound on post-drug withdrawal day-10 [5]. In contrast, Adam and Oswald's 1986 study in 12 volunteers reported increased stage II NREM after a 20 and 40 mg dose of promethazine; reduction in REM sleep was observed only with the 40 mg dose [6].

Borbély et al 1988 found a single bedtime dose (50 or 75 mg) of diphenhydramine in 10 adults increased motor activity without affecting any subjective sleep parameter [7]. Rickels et al's 1983 double-blind placebo-controlled study in 111 mildly to moderately insomniac patients also observed significant improvement in subjective sleep parameters after diphenhydramine (50 mg) administration in moderately insomniac patients [8].

2.2 Sedation

Insomnia is known as persistent problems falling and staying asleep. In children, it generally presents as bedtime resistance, difficulty initiating sleep, night wakings, or any combination of these symptoms [1].

Insomnia isn't discussed in detail in the remainder of this paper. The focus shifts to sedation, and the definitions and guidelines for sedation in children (where available) are discussed in this section.

2.2.1 New Zealand

The Starship Hospital guidelines for sedation in children defines sedation as follows:

> *"Sedation means the sedation of a patient for diagnostic, interventional, medical or surgical procedures, with or without local anaesthesia, for the purpose of producing a degree of sedation without loss of consciousness. Sedation includes the administration, by any route, of all forms of drugs which result in depression of the central nervous system".*

The guideline also states sedation should be employed for procedures that children find stressful or painful. There are suggested sedatives or agents in the guideline, none of which are sedating antihistamines.

The New Zealand Formulary (NZF) chapter on hypnotics (4.1.1) includes a section on antihistamines, stating:

> *"Some antihistamines (section 3.4.1) such as promethazine and diphenhydramine are used as hypnotics. Diphenhydramine is on sale as a Restricted (Pharmacist Only) Medicine to the public for occasional insomnia. The prolonged duration of action can often cause drowsiness the following day. The sedative effect of antihistamines may diminish after a few days of continued treatment; antihistamines are associated with headache, psychomotor impairment and antimuscarinic effects. Promethazine may cause paradoxical excitation in children and the elderly. Overdose can lead to serious cardiac arrhythmias and death."*

Unlike the NZF, the New Zealand Formulary for Children (NZFC) chapters on hypnotics (4.1.1) and sedative and analgesic peri-operative drugs (15.1.4) don't include information on, or links to sedating antihistamines. However, the promethazine monograph includes dosing regimens for children from the age of 2 years for sedation (short-term use).

The anaesthesia, sedation, and resuscitation in dental practice chapter (15.1) of the NZFC links to the New Zealand Dental Council's website, and their sedation practice standard (April 2017) sets minimum standards

for the practice of minimal and moderate sedation in dentistry. Minimal and moderate sedation are defined as follows:

> *"Minimal sedation is a drug-induced state during which the patient responds normally to verbal commands. Cognitive function and physical co-ordination may be impaired but airway reflexes, cardiovascular and ventilatory functions are unaffected.*
>
> *Moderate sedation is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation, throughout the period of sedation. The patient has the ability to maintain their airway patency on request, spontaneous ventilation is adequate and cardiovascular function is usually maintained."*

The practice standard states sedation may be achieved by a wide variety of medicines and techniques, and may accompany techniques for pain management such as local anaesthetic. In dental practice the most common sedation techniques are inhalation using nitrous oxide/oxygen, oral, and intravenous (IV). Oral sedation should only be used for an intended level of minimal sedation. The practice standard sets core principles for sedation for dental procedures, but it doesn't contain guidance or recommendations on the specific medicines that should be used.

Courses for dental practitioners as well as the representation of dental practitioners who practice sedation dentistry is through the New Zealand society for sedation in dentistry (NZSSD). Publicly available guidance for sedation during dental procedures from the NZSSD could not be found.

The bpac^{nz} article on travel consultation essentials (2015) includes advice for people travelling with medicines, vaccination recommendations and maintaining good health. There is information on reducing symptoms of jetlag in this article. Adequate fluid intake and avoidance of caffeine and alcohol are recommended for travellers in transit, and immediate-release melatonin has evidence for reducing jetlag. There is no information on travelling with children, or information on sedation.

A New Zealand Herald news article on the medicines to pack for your overseas holiday (April 2018) includes a section on medicines for sleep. It states that prescription sleeping medicines may be recommended by a doctor for short-term use. Alternatively, over-the-counter sleeping medicines like the sedating antihistamines doxylamine are available from a pharmacy. Sedating antihistamines should not be used for children when flying.

Comments:
Guidelines suggest sedation in children can be considered for diagnostic, interventional, medical or surgical procedures, including dental procedures. There could be anecdotal evidence suggesting oral sedating antihistamines may be used during travel, such as for sedation on long-haul flights, but this doesn't appear to be supported by clinical guidelines or information in lay media.
As with any topic on the abuse, misuse or off-label use of medicines, the problem can be difficult to quantify because regulatory mechanisms to capture this information are limited.

2.2.2 International

The NICE guidance for sedation in under 19s (published 15 December 2010, checked December 2018) states no medicines have a UK marketing authorisation specifically for sedation in people under 19 years. Prescribers should follow relevant professional guidance, taking full responsibility for the decision, and consulting with experts as needed. This guidance includes some recommendations for procedures such as painless imaging, painful procedures, dental procedures and endoscopy, none of which include sedating antihistamines.

The American Academy of Pediatrics (AAP) guidelines for monitoring and management of paediatric patients before, during, and after sedation (updated in 2016) was developed by the AAP and the American Academy of Pediatric Dentistry (AAPD). Medicines that have a long duration of action (eg, intramuscular pentobarbital, phenothiazines) have fallen out of favour because of unpredictable responses and prolonged recovery. The use of these medicines require a longer period of observation even after the child achieves currently used

recovery and discharge criteria. In particular, promethazine has a "black box warning" regarding fatal respiratory depression in children <2 years of age.

The Royal Children's Hospital Melbourne factsheet on sedation for procedures (2018) includes a section on types of sedatives, none of which are sedating antihistamines. Nitrous oxide, ketamine, midazolam and chloral hydrate are mentioned.

2.3 Oral sedating antihistamines

Sedating antihistamines contained in products for oral use that are currently marketed in New Zealand include brompheniramine, chlorphenamine (chlorpheniramine), cyclizine, dexchlorpheniramine, diphenhydramine, doxylamine, meclozine and promethazine. Of these, diphenhydramine and doxylamine are contained in products for insomnia and/or a sleep aid from the age of 12 years, and promethazine is contained in products for sedation from the age of 2 years.

The required warning statements for labels of all over-the-counter oral sedating antihistamine products since 1 June 2019 are:

- Do not use in children under 2 years old.
- This medicine may cause drowsiness.
- Be cautious about driving a vehicle or operating machinery within 8 hours of taking this medicine.

In addition, labels for sedating antihistamines when used for the treatment of insomnia require the following warning statements since 16 August 2019:

- Do not use in children under 12 years old.
- Do not exceed the maximum stated dose.
- This product is for temporary use only. [or] For short term use only.
- Consult a doctor if sleeplessness persists.

Drowsiness is a significant side effect with sedating antihistamines although paradoxical stimulation may occur, especially with high doses or in children and the elderly [9]. Drowsiness may reduce after a few days of treatment and is less of a problem with the newer non-sedating antihistamines [9].

Adverse effects that are more common with sedating antihistamines include headache, psychomotor impairment and anticholinergic effects such as urinary retention, dry mouth, blurred vision and gastrointestinal disturbances [9]. Other rare adverse effects include hypotension, palpitation, arrythmias, extrapyramidal effects, dizziness, confusion, depression, sleep disturbances, tremor, convulsions, and hypersensitivity reactions (including bronchospasm, angioedema, anaphylaxis, rash) [9].

A summary of products containing diphenhydramine, doxylamine or promethazine is shown in Table 1.

Table 1: Summary table of products containing diphenhydramine, doxylamine or promethazine*

Product	Indications	Dose	Class
Unisom SleepGels (diphenhydramine HCl 50 mg)	Data sheet: A night time sleep aid for the short-term management of insomnia Label: Night time sleep aid	Data sheet: Adults and children over 12 years of age: One softgel (50 mg) at bedtime if needed. Label: Adults and children over 12 years of age: One softgel (50 mg) at bedtime if needed, or as directed by a doctor.	Restricted
Dozile (doxylamine succinate 25 mg)	Data sheet: Temporary use in the relief of insomnia Label: No label in electronic file	Data sheet: Adults: 1 capsule 30 minutes before retiring, or as directed by a pharmacist or physician. Not recommended for children under 12 years of age	Restricted
Allersoothe (Elixir: promethazine hydrochloride 1 mg/mL Tablets: promethazine hydrochloride 10 mg, 25 mg)	Data sheet (elixir and tablets): Sedation - for short term use under the advice of a doctor or pharmacist. Do not use for more than 7-10 consecutive days Label (elixir): For short term use for sedation, on the advice of a doctor or pharmacist. Do not use for more than 7-10 consecutive days. Label (tablets): No labels in electronic file	Data sheet (elixir and tablets): Give as single dose at night • 2-5 years: 5-15 mg (5-15 mL) • 6-12 years: 10-25 mg (10-25 mL) • over 12 years and adults: 25-75 mg Label (elixir): Single dose at night • 2-5 years: 5-15 mL • 6-12 years: 10-25 mL	Restricted
Phenergan (Elixir: promethazine hydrochloride 1 mg/mL Tablets: promethazine hydrochloride 10 mg, 25 mg)	Data sheet (elixir): Sedation: For short term use under the advice of a doctor or pharmacist. Do not use for more than 7 to 10 consecutive days. Label (elixir): For short term use for sedation, on the advice of a doctor or pharmacist. Do not use for more than 7-10 consecutive days. Label (tablets): Sedation for short term use under the advice of a doctor or pharmacist. Do not use for more than 7 to 10 consecutive days.	Data sheet (elixir and tablets): Given as a single dose at night • 2-5 years: 5-15 mg (5-15 mL) • 6-12 years: 10-25 mg (10-25 mL) • adults: 25-75 mg Label (elixir): Single dose at night • 2-5 years: 5-15 mL • 6-12 years: 10-25 mL Label (10 mg tabs): Single nightly dose • 6-12 years: 1-2 tablets Label (25 mg tabs): Single dose • 6-12 years: Not recommended for children less than 12 years except on medical advice.	Restricted

* only information relating to insomnia, sleep or sedation is included in this table

Comments:

The dosing of promethazine elixir (both Allersoothe and Phenergan) overlaps by 5 mg for children aged 2-5 years and children aged 6-12 years (ie, potentially a 15 mg dose for a 5-year-old and a lower dose of 10 mg for a 6-year-old). In addition, the instructions to give as a single dose at night implies use for insomnia.

2.3.1 Diphenhydramine

Diphenhydramine is an ethanolamine antihistamine with anticholinergic and sedative effects [10]. The primary action of diphenhydramine is the antagonism of certain effects of histamine such as bronchoconstriction and capillary dilation [10].

The most frequently experienced secondary effects of diphenhydramine relate to central nervous system depression [10]. Effects vary from slight drowsiness to deep sleep and have been reported to include the inability to concentrate, lassitude, dizziness, muscular weakness and incoordination [10]. However, the sedative action of diphenhydramine has been found to be of some value for occasional use in the relief of nighttime sleeplessness [10]. The sedative action may last up to 6 hours but often diminishes after a few days as tolerance to this effect develops [10].

Other actions of diphenhydramine include an antiemetic effect and some anticholinergic activity which can produce blurred vision, dry mouth, and gastrointestinal disturbances (eg, nausea, vomiting, epigastric pain, diarrhoea) [10].

There is currently one product on the market that contains diphenhydramine: Unisom SleepGels. The indication in the data sheet is described as a night time sleep aid for the short-term management of insomnia. The label states it's a night time sleep aid (Figure 1). Dose instructions in the data sheet and label are one softgel (50 mg) at bedtime if needed for adults and children over 12 years of age. The age restriction is in line with the warning statements required for oral sedating antihistamines when used for insomnia.

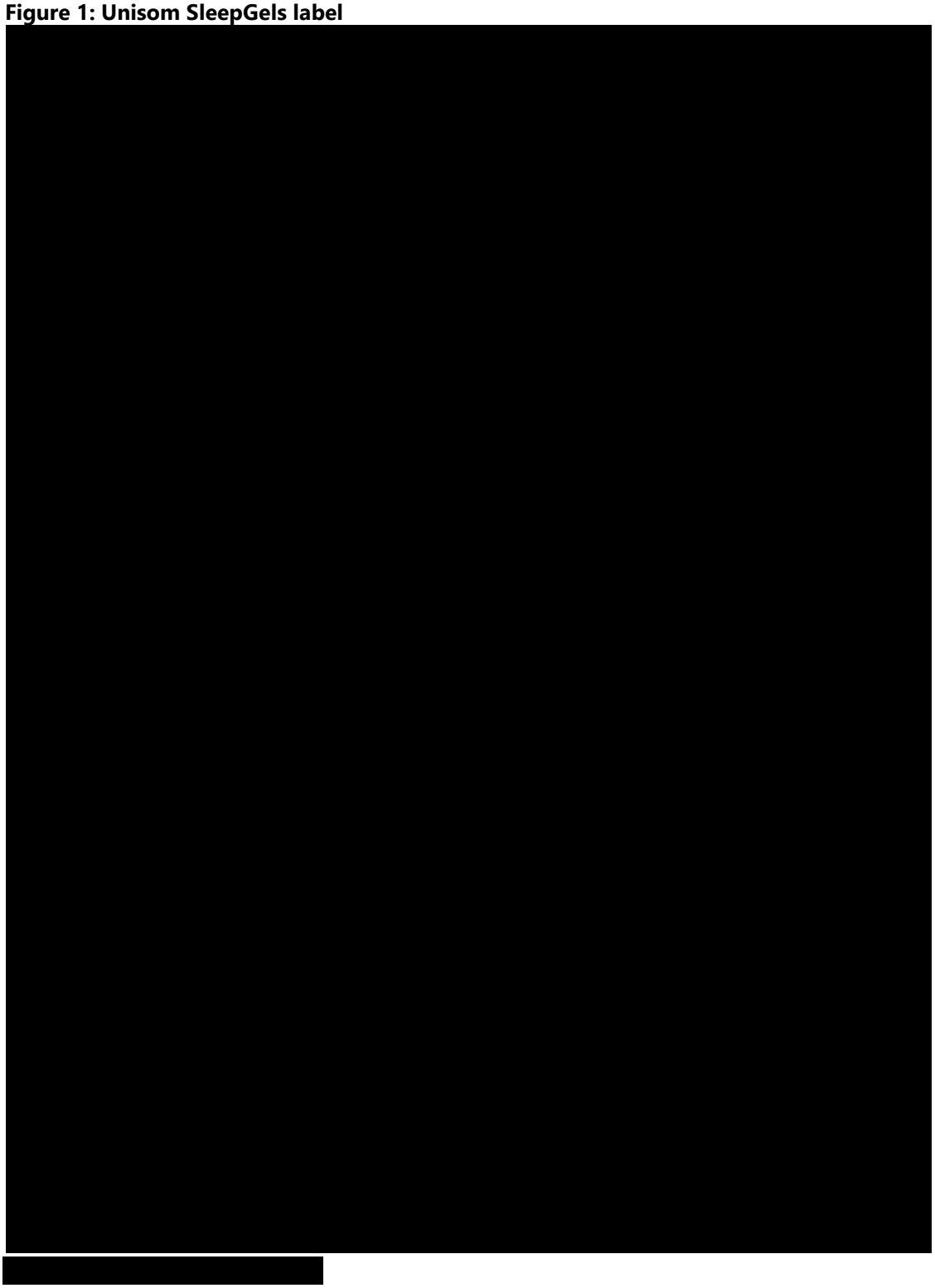
Unisom SleepGels is a restricted (pharmacist only) medicine in line with the classification statement for diphenhydramine (Table 2).

Table 2: Diphenhydramine classification statements

Ingredient	Conditions (if any)	Classification
Diphenhydramine	**except** when specified elsewhere in this schedule	Prescription
Diphenhydramine	for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of insomnia; for oral use for the treatment of insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units	Restricted
Diphenhydramine	for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing diphenhydramine or when at least 1 of the other active ingredients is a sympathomimetic decongestant; for oral use in a sealed container of not more than 10 tablets or capsules for the prevention or treatment of motion sickness in adults and children over 2 years of age **except** when sold at a transport terminal or aboard a ship or aircraft	Pharmacy Only

Source: Medsafe Classification Database (www.medsafe.govt.nz/profs/class/classintro.asp)

Figure 1: Unisom SleepGels label



2.3.2 Doxylamine

As with diphenhydramine, doxylamine succinate is an ethanolamine derivative antihistamine [11]. Doxylamine is an antihistamine with hypnotic, anticholinergic, antimuscarinic and local anaesthetic effects [11]. It has a duration of action of 6 to 8 hours [11].

It is used for the temporary relief of sleeplessness due to its sedative effect [11]. Doxylamine is not structurally related to the cyclic antidepressants [11].

There is currently one product that contains doxylamine marketed for insomnia: Dozile. The indication in the data sheet is described as temporary use in the relief of insomnia. Dose instructions in the data sheet is one capsule 30 minutes before retiring, or as directed by a pharmacist or physician for adults; not recommended for children under 12 years of age. The age restriction is in line with the warning statements required for oral sedating antihistamines when used for insomnia.

There is no label for Dozile in its electronic product file.

Dozile is a restricted (pharmacist only) medicine in line with the classification statement for doxylamine (Table 3).

Table 3: Doxylamine classification statements

Ingredient	Conditions (if any)	Classification
Doxylamine	**except** when specified elsewhere in this schedule	Prescription
Doxylamine	for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of insomnia; for oral use for the treatment of insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units	Restricted
Doxylamine	for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing doxylamine or when at least 1 of the other active ingredients is a sympathomimetic decongestant	Pharmacy Only

Source: Medsafe Classification Database (www.medsafe.govt.nz/profs/class/classintro.asp)

2.3.3 Promethazine

Promethazine is a phenothiazine derivative [12]. However, it differs from antipsychotic phenothiazines by the presence of a branched side chain and the absence of ring substitution. This structure is responsible for its lack of dopaminergic action and subsequent lack of antipsychotic effect.

Promethazine is a long acting antihistamine with mild atropine-like anticholinergic effects and some anti-serotonin effects [12]. Because of its marked effect on the CNS, it acts as an antiemetic, hypnotic, tranquiliser and a potentiator of anaesthetics, hypnotics, sedatives and analgesics [12]. Promethazine's antihistamine action has been reported to be between 4 and 12 hours [12].

Information on paediatric use in the data sheet states [12]:

> *"Children may experience paradoxical excitation with promethazine.*
>
> *The use of promethazine should be avoided in children and adolescents with signs and symptoms suggestive of Reye's Syndrome.*
>
> *This product must not be used in children under 2 years of age, due to the potential for fatal respiratory depression (see Section 4.3 Contraindications).*
>
> *Caution should be exercised when administering promethazine to children as there is potential for central and obstructive apnoea and reduced arousal. Excessive dosages of antihistamines in children may cause hallucinations, convulsions and sudden death."*

There are currently two brands of products containing promethazine marketed for sedation: Allersoothe and Phenergan. Phenergan (innovator product) was first approved for use in New Zealand in December 1969. Due to its date of approval, it is likely that an assessment was never conducted as part of the approval process (ie, it was "grandfathered").

The indication for sedation in the data sheets is described as short-term use under the advice of a doctor or pharmacist; do not use for more than 7 to 10 consecutive days. Dose instructions in the data sheets is 5-15 mg (5-15 mL) at night for children aged 2-5 years and 10-25 mg (10-25 mL) for children aged 6-12 years.

The label for Allersoothe elixir is shown in Figure 2. It is interesting to note that the side panel listing the conditions it can be used for doesn't include sedation but the dosing information does (ie, these don't match up). There are no labels for Allersoothe tablets in the electronic product file.

The label for Phenergan elixir is shown in Figure 3 and labels for Phenergan tablets in Figures 4 and 5. Dosing instructions on the labels are in line with data sheets.

All these products are restricted (pharmacist only) medicines in line with the classification statements for promethazine (Table 4).

It is interesting to note that unlike Unisom SleepGels and Dozile which are indicated for insomnia in children aged 12 years and over, the promethazine products (Allersoothe, Phenergan) are indicated for sedation in children 2 years and over.

Table 4: Promethazine classification statements

Ingredient	Conditions (if any)	Classification
Promethazine	**except** when specified elsewhere in this schedule	Prescription
Promethazine	for oral use in medicines for adults or children over 2 years of age other than in medicines used for the treatment of insomnia; for oral use for the treatment of insomnia when sold in the manufacturer's original pack containing not more than 10 dosage units	Restricted
Promethazine	for oral use in medicines for adults and children over 6 years of age when combined in the same container with 1 or more other therapeutically active ingredients either when in the bedtime dose of a day/night pack containing promethazine or when at least 1 of the other active ingredients is a sympathomimetic decongestant; for oral use in a sealed container of not more than 10 tablets or capsules for the prevention or treatment of motion sickness in adults and children over 2 years of age **except** when sold at a transport terminal or aboard a ship or aircraft	Pharmacy Only

Source: Medsafe Classification Database (www.medsafe.govt.nz/profs/class/classintro.asp)

Figure 2: Allersoothe elixir label

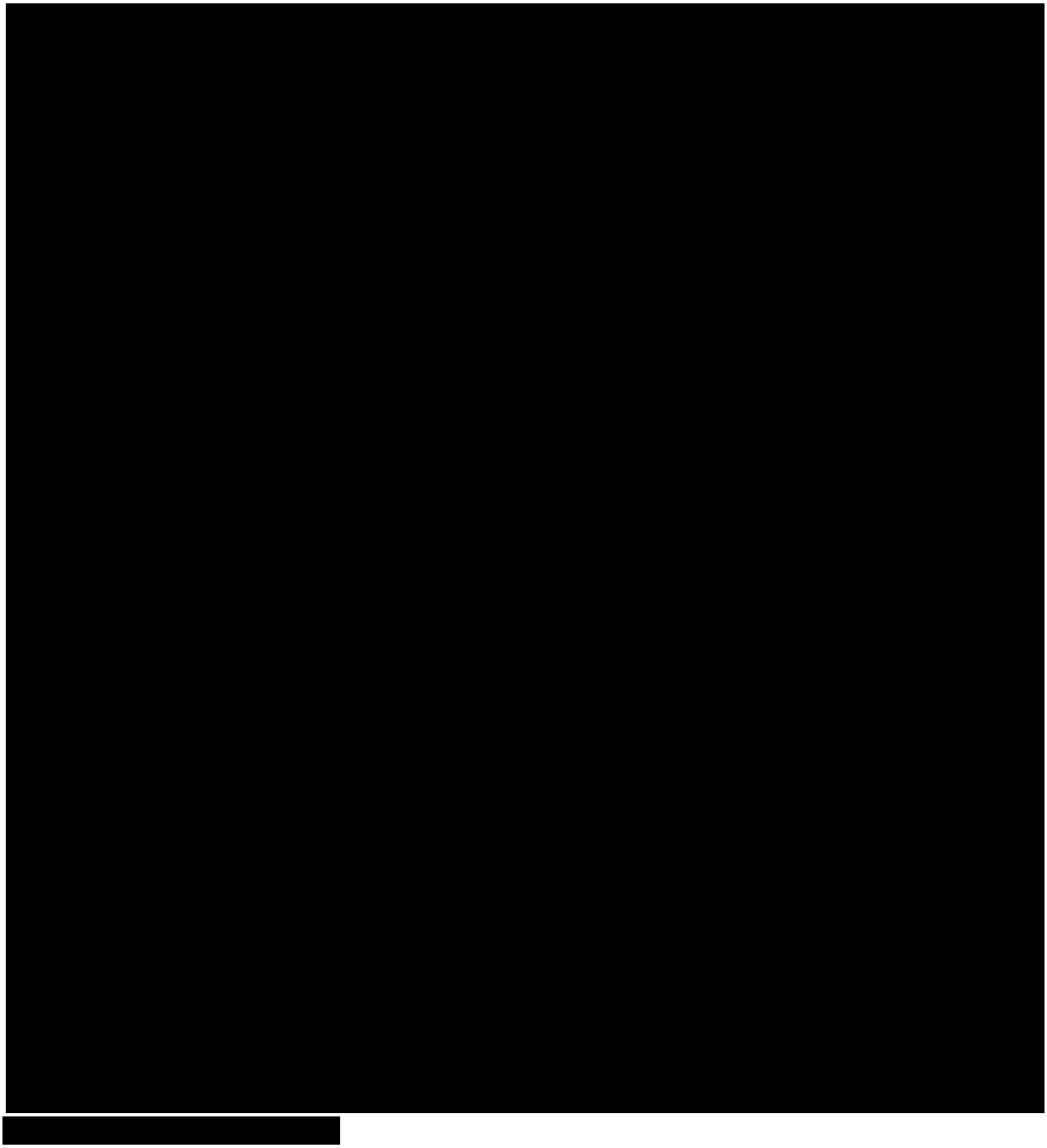


Figure 3: Phenergan elixir label

Figure 4: Phenergan 10 mg tablets label

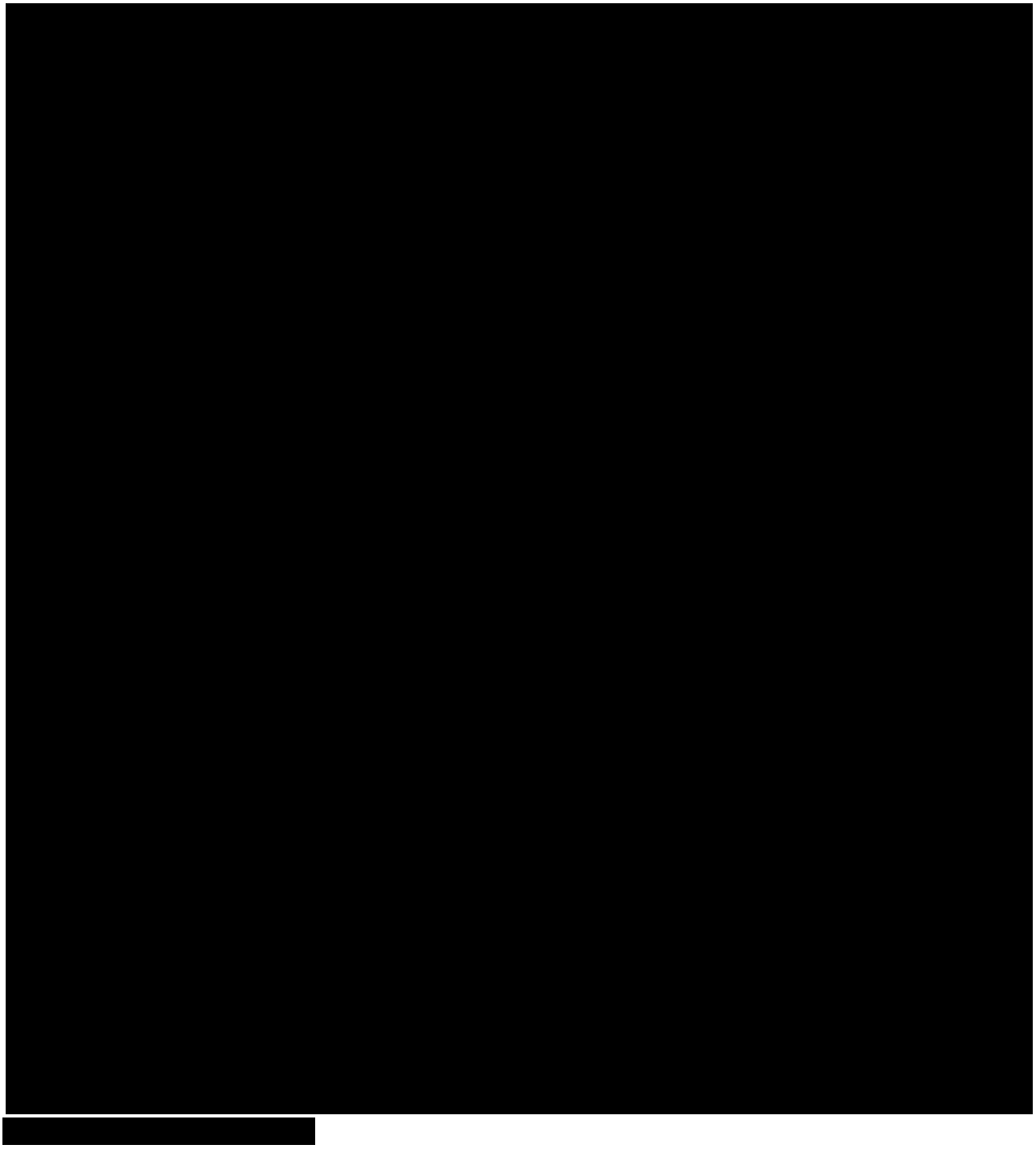
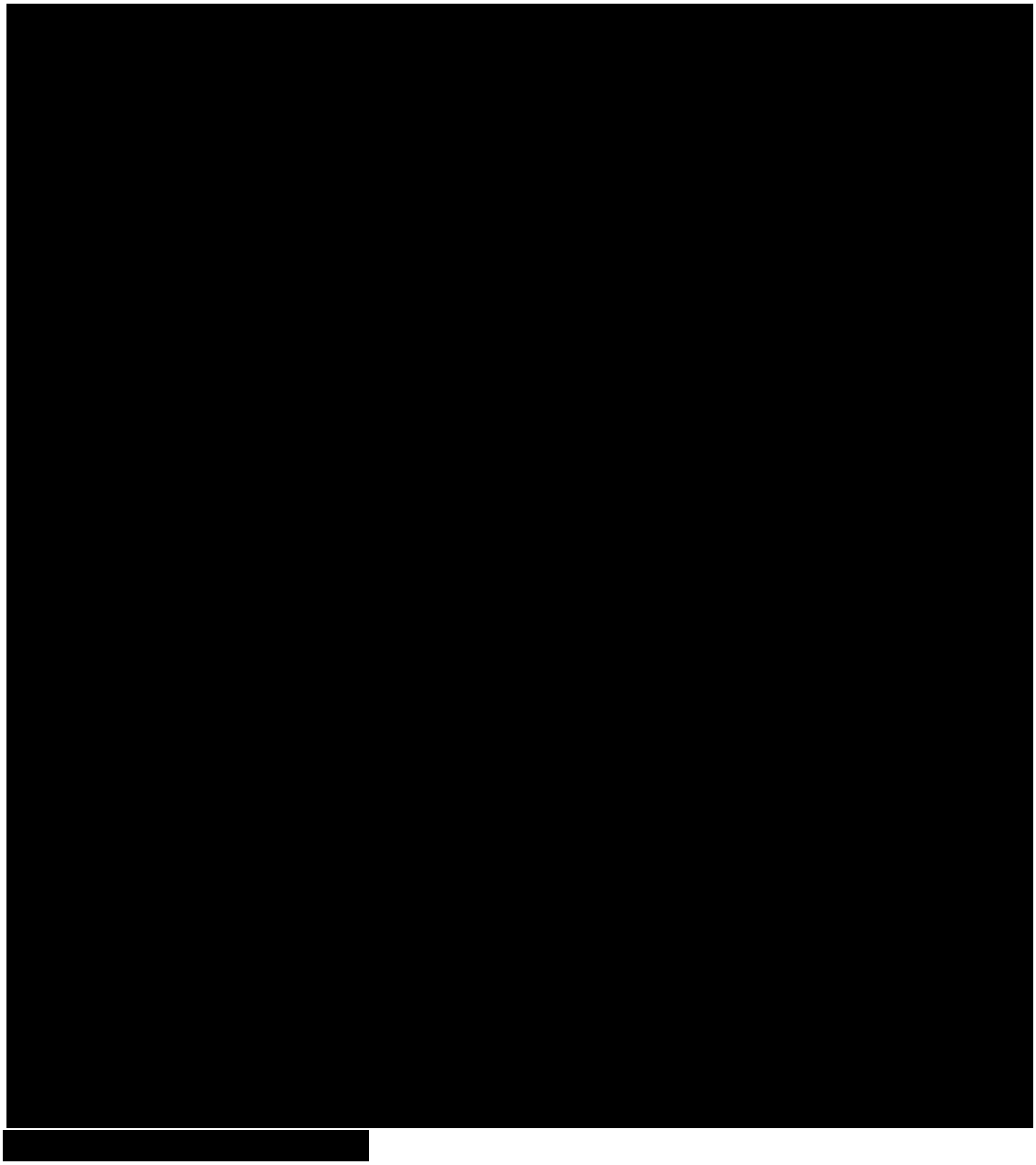


Figure 5: Phenergan 25 mg tablets label



3 SCIENTIFIC INFORMATION

3.1 Published literature

From information in the preceding sections of this paper, it can be seen that promethazine is currently the only oral sedating antihistamine that can be used in children aged 2 to <12 years for sedation. This literature section contains articles identified as discussing the use of promethazine for sedation and only the more recent or relevant articles are included.

3.1.1 Fong et al 2017 – Chloral hydrate as a sedating agent for neurodiagnostic procedures in children (Cochrane review) [13]

Although this review was predominantly about chloral hydrate, RCTs that assessed chloral hydrate against other sedative agents, including promethazine, for children undergoing non-invasive neurodiagnostic procedures were included.

A total of 13 studies involving 2390 children were included in this review. Most of the studies assessed 3 main outcome measures: proportion of children who were unsuccessfully sedated for the neurodiagnostic procedure, length of time taken for adequate sedation, and side effects associated with the sedative agent.

When compared with oral promethazine, children who received oral chloral hydrate had lower sedation failure (RR 0.11, 95% CI 0.01 to 0.82; 1 study, moderate-quality evidence). Children who received oral chloral hydrate had a shorter time to achieve adequate sedation when compared with those who received oral promethazine (MD -12.11, 95% CI -18.48 to -5.74; 1 study, moderate-quality evidence). A summary of results comparing chloral hydrate to promethazine is provided in Table 5.

The review suggests oral chloral hydrate is just as effective a sedative agent with similar sedation failure rate when compared with oral dexmedetomidine, oral hydroxyzine hydrochloride, and oral midazolam; and probably a more effective sedative agent with lower sedation failure rate when compared with oral promethazine. The side effect profile of oral chloral hydrate when compared to other sedatives requires further study.

3.1.2 Coté et al 2000 – Adverse sedation events in paediatrics: Analysis of medications used for sedation [14]

Using critical incident analysis of case reports, the authors performed a systematic investigation of medicines associated with adverse sedation events in paediatric patients.

118 case reports from the US FDA's adverse reporting system, the US Pharmacopoeia and results of a survey of paediatric specialists were used. Outcome measures were death, permanent neurologic injury, prolonged hospitalisation without injury, and no harm. This investigation examined the relationship between outcome and medicines: individual and classes of medicines, routes of administration, combinations and interactions, medication errors and overdoses, patterns of use, practitioners, and venues of sedation.

95 incidents fulfilled study criteria. The age range was 0.08 to 20 years (mean ± standard deviation: 5.7 ± 5.5). Of these 95 cases, 60 had adverse outcomes defined as death (n=51) or permanent neurologic injury (n=9). Review of adverse sedation events indicated there was no relationship between outcome and medicine class (opioids, benzodiazepines, barbiturates, sedatives, antihistamines, and anaesthetics) or route of administration.

Negative outcomes (death and permanent neurologic injury) were often associated with an overdose (n=28). Some overdoses were attributable to prescription/transcription errors. Negative outcomes were also associated with medicine combinations and interactions (n=44). The use of ≥3 sedating medicines compared with 1 or 2 medicines was strongly associated with adverse outcomes (18/20 vs. 7/70). Dental specialists had the greatest frequency of negative outcomes associated with the use of ≥3 sedating medicines.

Adverse events occurred despite medicines being administered within acceptable dosing limits. Negative outcomes were also associated with medicines administered by non-medically trained people and medicines administered at home. Some injuries occurred on the way to a facility after administration of sedatives at home, some took place in transport vehicles or at home after discharge from medical supervision. Deaths and injuries after discharge from medical supervision were associated with the use of medicines with long half-lives (chloral hydrate, pentobarbital, promazine, promethazine, chlorpromazine).

The observation that negative outcomes were associated with all medicine classes and all routes of administration suggests these negative outcomes occur not because of the medicines themselves but rather because of administration practices (combinations, errors, and monitoring standards).

Comments:
The age range for patients included in this paediatric study was up to 20 years. It is not known what the authors definition of paediatric patients was. The authors conclude that findings suggest the negative outcomes are more likely due to practice or administration issues rather than the medicine itself.

3.1.3 Hickson et al 1990 – Should promethazine in liquid form be available without prescription? [15]

This paper was published at a time when promethazine was only available on prescription, but an application had been made to the US FDA to approve liquid OTC allergy and cough/cold products containing promethazine as an active ingredient.

The authors note promethazine has been reported to cause significant sedation, agitation, hallucinations, seizures, dystonic reactions, and possibly apparent life-threatening events or sudden unexpected death of an infant (SUDI). These are relatively uncommon adverse reactions and would be unlikely to occur if parents use OTC promethazine only for appropriate indications in children over 2 years of age. However, research evaluating the use of various OTC medicines by families for their children indicate promethazine may be used inappropriately.

The authors state promethazine syrup's sedating effect is most likely to be the reason for misuse by parents. This most often occurs in a stressful environment with no intent to harm the child. Multiple agents are used such as alcohol, benzodiazepines, chloral hydrate, cocaine, codeine, phenobarbital and promethazine. Most infants sedated by their parents with or without their physicians' directions recover uneventfully, but a few probably experience life-threatening events or perhaps sudden death.

The availability of promethazine in a syrup form without a prescription may increase its use as a sedative for young infants by both parents and physicians. OTC availability implies a greater margin of safety compared to medicines available only on prescription. This and the ease of administration in liquid form could increase the use of promethazine by both physicians and parents for infants' irritability and colic.

The benefits and risks of promethazine OTC should be carefully weighed. It is an effective antihistamine and is relatively safe in older children, with millions of doses administered to paediatric patients. However, there are other OTC medicines that are as effective and safer than promethazine for its indicated uses in allergy, cough/cold products, and for travel sickness. Postoperative anti-nausea and vomiting properties do not apply to OTC considerations, and children whose parents believe need a sedative probably shouldn't get one without first consulting a physician. Therefore, the need for OTC promethazine even for older children is not compelling.

Comments:

The authors suggest that parents of children who require sedation should consult a doctor first.

3.2 CARM data

Up to 31 December 2019, there are 35 cases reported to CARM describing an adverse reaction to a sedating antihistamine in a patient aged 2 to <18 years (Annex 1). Table 6 shows the age groups of these 35 cases. Table 7 shows the medicines reported as suspect, with 18 of the 35 cases reporting an oral route of administration.

Table 6: Reports to CARM in patients aged 2 to <18 years, by age group

Age group (years)	Number of cases
2 to <6	3
6 to <12	12
12 to <18	20
Total	**35**

Table 7: Reports to CARM in patients aged 2 to <18 years, by medicine and oral route of administration

Medicine	Number of cases (total)	Number of cases (total via oral route)
brompheniramine	0	0
chlorphenamine	2	2
cyclizine	19	6
dexchlorpheniramine	1	1
diphenhydramine	2	2
doxylamine	1	0
meclozine	1	1
promethazine	9	6
Total	**35**	**18**

The eight cases reporting oral diphenhydramine or oral promethazine as the suspect medicine are shown in Table 8. All eight cases were reported as not serious. Of these eight cases, six were reported in a patient aged <12 years. Of the eight cases reported in the last 20 years, none reported insomnia or sedation as an indication for use in a patient aged <12 years.

Table 8: Reports to CARM where oral diphenhydramine or oral promethazine were reported as suspect

CARM ID	Date	Age	M/F	Medicine(s)	Reaction(s)	Notes
000786	Mar 1966	10	F	thioridazine, diazepam, pethidine*, hyoscine hydrobromide, promethazine*	convulsions grand mal, apnoea	[redacted]
001234	Feb 1968	7	M	promethazine*, doxycycline*	hallucination	[redacted]
014064	Oct 1985	4	F	dicyclomine*, promethazine*	tooth disorder	[redacted]
016379	Aug 1987	12	M	diphenhydramine*, ammonium chloride, sodium citrate	urticaria	[redacted]
056968	Jul 2003	8	M	promethazine*	hallucination, tremor, disorientation, confusion	[redacted]
105233	Jan 2013	10	F	promethazine* (Allersoothe 1 mg/mL elixir)	product problem, nausea	[redacted]
114636	Dec 2014	11	M	diphenhydramine*	confusion, agitation, hallucination, mydriasis, fever	[redacted]
114925	Jan 2015	12	F	promethazine* (Allersoothe)	hallucination, confusion, sleep disturbed, somnambulism, nervousness	[redacted]

* suspect medicine

4 DISCUSSION AND CONCLUSIONS

There are a number of oral sedating antihistamines that are currently marketed in New Zealand. Of these, diphenhydramine and doxylamine are contained in products for insomnia and/or a sleep aid from the age of 12 years, and promethazine is contained in products for sedation from the age of 2 years. This paper therefore focused on these three sedating antihistamines, particularly on promethazine. All are restricted (pharmacist only) medicines, therefore available OTC but not available for self-selection, and there must be a consultation with a pharmacist at the time of purchase.

The use of promethazine for sedation from the age of 2 years is contained in data sheets and labels of products despite oral sedating antihistamines being contraindicated in children under 12 years of age when used for insomnia. Phenergan (promethazine innovator product) was "grandfathered" in New Zealand in 1969. It has a long history of use and many other oral antihistamines, both sedating and non-sedating, have since been approved.

Guidelines both here and internationally do not appear to recommend oral sedating antihistamines for the sedation of children. There is limited recent information in the literature relating to promethazine and its use in children for sedation. As with any topic on the abuse, misuse or off-label use of medicines, it is difficult to know if oral sedating antihistamines are being used for sedation in children, and if so, to quantify the scale of use.

Although the only products currently on the market for sedation in children from the age of 2 years are those containing promethazine, any recommendations by the Committee should apply to all oral sedating antihistamines.

5 ADVICE SOUGHT

The Committee is asked to advise on the following:

- Should the use of oral sedating antihistamines in children for sedation (currently from the age of 2 years) be increased to an older age? If so, what age should this be?
- Does this require further communication other than MARC's Remarks in *Prescriber Update*?

6 ANNEXES

1. Line listing of reports to CARM [confidential]

7 REFERENCES

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