Medicines Adverse Reactions Committee

Meeting date	8/06/2023	Agenda item	3.2.2
Title	**Safety and efficacy of pholcodine**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Benzydamine + Cetylpyridinium + Pholcodine	Difflam Plus Cough Sore Throat Lozenges Lozenge, Sugar Free Honey, Lemon & Ginger Flavour	iNova Pharmaceuticals (New Zealand) Limited
Benzydamine + Cetylpyridinium + Pholcodine	Difflam Plus Cough Sore Throat Lozenges Lozenge, Sugar Free Pineapple & Lime Flavour	iNova Pharmaceuticals (New Zealand) Limited
Benzydamine + Cetylpyridinium + Pholcodine	Difflam Plus Dry Cough + Antibacterial + Anti-inflammatory Lozenge, Blackcurrant Flavour Sugar Free	iNova Pharmaceuticals (New Zealand) Limited
Bromhexine + Pholcodine	Duro-Tuss Cough Liquid Expectorant Oral solution, 0.8mg/1mg per mL	iNova Pharmaceuticals (New Zealand) Limited
Cetylpyridinium + Pholcodine	Duro-Tuss Dry Cough Lozenge, (Lemon)	iNova Pharmaceuticals (New Zealand) Limited
Cetylpyridinium + Pholcodine	Duro-Tuss Dry Cough Lozenge, (Orange)	iNova Pharmaceuticals (New Zealand) Limited
Pholcodine	Duro-Tuss Dry Cough Liquid Forte Oral solution, 3 mg/mL	iNova Pharmaceuticals (New Zealand) Limited
Pholcodine	Duro-Tuss Dry Cough Liquid Junior Oral solution, 1 mg/mL, New Formula	iNova Pharmaceuticals (New Zealand) Limited
Pholcodine	Duro-Tuss Dry Cough Liquid Regular Oral solution, 1 mg/mL, New Formula	iNova Pharmaceuticals (New Zealand) Limited
Phenylephrine + Pholcodine	Duro-Tuss Phenylephrine PE Dry Cough + Nasal Decongestant Oral solution	iNova Pharmaceuticals (New Zealand) Limited
Pholcodine	Pholcodine Linctus BP Linctus, 5 mg/5mL, (AFT)	AFT Pharmaceuticals Ltd
Pholcodine	Strong Pholcodine Linctus BP Linctus, 10 mg/5mL, Pinewood	AFT Pharmaceuticals Ltd
Pholcodine	Pholcodine Linctus BP Linctus, 5 mg/5mL, (PSM) (not available)	Noumed Pharmaceuticals Limited

Pholcodine	Pholcodine Strong BP Linctus, 10 mg/5mL, (PSM) (not available)	Noumed Pharmaceuticals Limited
Pholcodine	Stubborn Dry Tickly Cough (Pharmacy Health) Linctus, 2 mg/mL (not available)	Noumed Pharmaceuticals Limited
PHARMAC funding	AFT Pholcodine Linctus BP Oral 1 mg/1mL is funded on the Hospital Medicines List	
Previous MARC meetings	132nd meeting December 2007: Safety and efficacy of cough and cold medicines for use in children. 138th meeting June 2009: Safety and efficacy of cough and cold medicines for use in children. 143rd meeting September 2010: Consideration of antitussive-expectorant and antitussive-mucolytic combination cough and cold medicines under Section 36 of the Medicines Act 1981. 180th meeting December 2019: Pholcodine: benefit-risk review.	
International action	European Medicines Agency: revocation on 6 March 2023. Therapeutics Goods Administration: recall notice on 28 February 2023, cancellation of pholcodine on 29 March 2023. Medicines and Healthcare products Regulatory Agency: recall and withdrawal from UK market. Malaysia National Pharmaceutical Regulatory Agency: cancellation of product registration and recall.	
Classification	Pharmacist-only medicine	
Advice sought	**The Committee is asked to advise whether:** • The evidence of an association between pholcodine use and an increased risk of anaphylaxis from NMBAs is now sufficient to require regulatory action? • In line with the section 35 of the Medicines Act 1981 (the Act) procedure, if pholcodine: o no longer can be regarded as a medicine that can be administered or used safely for the symptomatic relief of dry (non-productive) cough OR o the efficacy of pholcodine no longer can be regarded as satisfactory • OR whether regulatory action not related to the Act best fits the information reviewed in this paper (for example changes to the data sheet)?	

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1 PURPOSE

In December 2019, the Medicines Adverse Reactions Committee (MARC) reviewed the risks and benefits of pholcodine. At that time, the Committee considered that the risk-benefit balance of pholcodine was marginal but there was insufficient evidence to indicate an unfavourable risk-benefit balance.

The available evidence on the association between prior pholcodine exposure and an increased risk of anaphylaxis with neuromuscular blocking agents (NMBAs) was included in the review. The Committee considered that although there was no clear causal association, there was some data on an ecological association. The Committee noted that the European Medicines Agency (EMA) had reviewed this issue in 2011 where they considered the association to be circumstantial and not entirely consistent which warranted further investigation through a case-control study.

In 2022, the results of this case-control study (ALPHO study) became available. The results of the ALPHO study together with a more recent observational study by Sadleir et al (2021) prompted regulators in Europe, United Kingdom, Australia and Malaysia to withdraw pholcodine-containing medicines from the market.

In light of the new information, the Committee is asked to review the evidence on the safety and efficacy of pholcodine and to consider whether pholcodine no longer can be regarded as a medicine that can be administered or used safely for the symptomatic relief of dry (non-productive) cough, and/or that the efficacy of pholcodine no longer can be regarded as satisfactory.

2 BACKGROUND

2.1 Pholcodine

Pholcodine is a morphinane alkaloid that is a derivative of morphine with a 2-morpholinoethyl group at the 3-position. It is an opiate acting directly on the cough centre of the central nervous system [1].

In New Zealand, pholcodine is a 'grand-fathered' medicine, as it was already in use when the Food and Drug Act 1969 and subsequent Medicines Act 1981 came into force. Pholcodine is indicated for the temporary relief of dry (non-productive) cough in children and adults 6 years and older [2].

Pholcodine is a pharmacist only medicine and is available in several different formulations, either as a single active ingredient or in combination with other active ingredients in cough and cold medicines.

2.2 Previous actions taken in New Zealand

November 2018 – Medicines Classification Committee 61st meeting

The Medicines Classification Committee (MCC) considered the reclassification of various cough medicines to a more restricted category in 2018. The MCC agreed that pholcodine has limited potential for abuse. A rare but potentially fatal association with anaphylaxis and neuromuscular blockers was noted but the evidence for this was considered limited. The MCC concluded that there were minimal safety concerns around pholcodine and that the current classification was appropriate.

The MCC suggested that Medsafe should review the risk-benefit profile and efficacy of pholcodine. This was taken to the 180th MARC meeting for advice.

December 2019 – Medicines Adverse Reactions Committee 180th meeting

The Committee discussed the available evidence on prior pholcodine exposure and NMBA-induced anaphylaxis. The Committee considered that although there was no clear causal association, there was some data on an ecological association. The Committee acknowledged concerns from the sector that widespread availability of pholcodine may be responsible for sensitisation to NMBAs. Anaphylaxis could be a very serious, sometimes fatal, reaction.

The MARC recommended that the MCC should consider reclassifying this medicine to a more restricted classification and pharmacists should primarily inform patients of the risk of harms, including the risk of anaphylaxis. The need to raise awareness with healthcare professionals around this issue was also discussed.

Overall, the MARC considered that the risk-benefit balance of pholcodine was marginal but there was insufficient evidence to indicate an unfavourable risk-benefit balance.

October 2020 – 65th Medicines Classification Committee 65th meeting

The MCC recommended that the change in classification of pholcodine from pharmacy-only to a restricted (pharmacist-only) medicine. The aim was to reduce use of pholcodine when it may not be indicated, and thereby reduce the potential risk of harm.

1 December 2022 – Gazette publication

On 1 December 2022, the pholcodine re-classification notice was published in the *New Zealand Gazette:*

> *Restricted Medicines*
>
> *Pholcodine; in medicines for oral use containing not more than 15 milligrams of pholcodine per solid dosage unit or per dose of liquid with a maximum daily dose not exceeding 100 milligrams of pholcodine, when combined with 1 or more active ingredients in such a way that the substance cannot be recovered by readily applicable means, or in a yield that would constitute a risk to health, when sold in a pack approved by the Minister or the Director-General for distribution as a restricted medicine.*

2.3 Cough: pathophysiology, causes of cough in adult and children and treatment options

Cough

Cough is an important protective reflex, but when persistent it is the most common reason why patients seek medical attention. Cough is associated with significantly impaired health-related quality of life. Sleep disturbance, nausea, chest pains, and lethargy occur frequently, and patients with chronic cough often experience social embarrassment, urinary incontinence, and low mood [3].

People often seek OTC cough medicines for themselves or their children, and many health professionals in primary care settings recommend them to their patients as a first-line treatment, despite there being little evidence as to whether these medicines are effective [3].

A national telephone survey of medication use in the US indicated that in a given week, 10% of children are given an OTC cough preparation by their carers [3].

Cough reflex

Each cough occurs through the stimulation of a complex reflex arc (Figure 1). This is initiated by the irritation of cough receptors that exist not only in the epithelium of the upper and lower respiratory tracts, but also in the pericardium, oesophagus, diaphragm and stomach [3].

- Chemical receptors sensitive to acid, cold, heat, capsaicin-like compounds, and other chemical irritants trigger the cough reflex via activation of ion channels of the transient receptor potential vanilloid type 1 (TRPV1) and transient receptor potential ankyrin type 1 (TRPA1) classes.
- Mechanical cough receptors can be stimulated by triggers such as touch, displacement or acidity.

Laryngeal and tracheobronchial receptors respond to both mechanical and chemical stimuli.

Impulses from stimulated cough receptors traverse an afferent pathway via the vagus nerve to a "cough centre" in the medulla, which itself may be under some control by higher cortical centres [3].

The cough centre generates an efferent signal that travels down the vagus, phrenic, and spinal motor nerves to expiratory musculature to produce the cough [3]. During vigorous coughing, intrathoracic pressures may reach 300 mm Hg and expiratory velocities approach 500 miles per hour [4]. While these pressures and

velocities are responsible for the beneficial effects of cough on mucus clearance, they are also responsible for many of the complications of cough, including exhaustion, self-consciousness, insomnia, headache, dizziness, musculoskeletal pain, hoarseness, excessive perspiration, urinary incontinence, cough-induced fractures, and concern that "something is wrong" [4].

[redacted]

Cough in adults [5]

Cough can be classified based on its duration: acute, subacute or chronic.

- *Acute cough* exists for less than 3 weeks and is most commonly due to an acute respiratory tract infection. Other causes include acute exacerbation of underlying chronic disease (eg, asthma, pneumonia, heart failure).
- *Subacute cough* lasts for 3 to 8 weeks and is usually due to a post-infectious cough (eg, respiratory viruses, pertussis, COVID-19) and exacerbations of underlying chronic diseases.
- *Chronic cough* lasts longer than 8 weeks. The most common causes include asthma, non-asthmatic eosinophilic bronchitis, chronic obstructive pulmonary disease (COPD), gastroesophageal reflux disease, and upper airway cough syndrome (due to postnasal drip). However, a number of other important aetiologies must also be considered in patients presenting with persistent cough, including ACE inhibitors/medicines known to cause cough, disorders affecting the airways (bronchiectasis, neoplasm, foreign body) or the pulmonary parenchyma (interstitial lung disease, lung abscess).

Cough in children

The most common cause of cough in children is a viral upper respiratory tract infection [6].

Cough in children can be categorised as acute (lasting less than 2 weeks), subacute or persisting (lasting 2-4 weeks) or chronic cough (lasting more than 4 weeks). Acute and sub-acute cough is usually due to a viral respiratory tract infection that will spontaneously resolve within 1 to 3 weeks in 90% of children [6].

An acute cough may also indicate the start of a chronic cough condition. In some cases, chronic cough lasting more than four weeks is caused by recurrent viral infections over winter, each incompletely resolving before the next infection. A careful history should distinguish this from true chronic cough, where causes may include the entire paediatric pulmonology spectrum. Children with chronic cough are likely to require review as the underlying cause of the cough may not initially be clear and the type of cough may change over time [6].

Treating coughs

Prior to prescribing treatment for cough, it is important to consider the underlying cause. Although the most common cause of a cough is a viral illness, a cough may be a symptom of an underlying disorder as described above [7].

When there is no identifiable cause, cough suppressants may be useful, for example if sleep is disturbed [7].

The majority of cough and cold medicines are contraindicated in children under 6 years of age [8].

Coughs associated with a viral illness

In most cases, treatment for cough is not necessary. Coughs associated with a viral illness are mild, short-term and self-limiting [9].

Cough medicines are marketed to provide symptomatic relief but do not help the underlying cause. A 2014 Cochrane review assessing the effects of oral OTC cough medicines in children and adults in community settings compared to placebo found no good evidence either for or against the effectiveness of OTC cough medicines. Many published studies were poorly reported, making it difficult to assess risk of bias. The studies were also very different from each other, making evaluation of overall efficacy difficult. High-quality randomised controlled trials of OTC cough preparations are needed [10].

Despite the wide use of cough medicines, there is little evidence to suggest they are any more effective than simple home remedies (eg, honey and warm drinks) (Table 1) [9, 11].

In New Zealand, cough suppressants containing an active pharmaceutical ingredient include pholcodine, codeine and dextromethorphan (Table 2) [9].

Table 1: Pharmacological options for dry cough (pholcodine not included)

Medicine (medicine classification)	**Age indication**	**Evidence of efficacy and other considerations**
Codeine (prescription only)	Should be avoided in children under 12 years of age. Relief of non-productive cough is not listed as an indication in the New Zealand codeine data sheet. The New Zealand Formulary states the adult dose is 10 – 20 mg 4-6 hourly; maximum 120 mg a day [12].	There is limited evidence supporting the use of codeine in acute cough in both adults and children. Positive results for the use of codeine in suppressing cough are based on small trials from the 1960s and have not since been replicated in larger trials. In addition, codeine is a prodrug for morphine, which requires additional considerations due to the risk of toxicity [3]. Codeine is constipating and can cause dependence [7].
Dextromethorphan (pharmacist-only)	Children 12 years and older [3]	Most efficacy studies for dextromethorphan were published before 2000. Many of the studies were considered to have serious design flaws making comparison between studies difficult. There is limited evidence supporting the use of this medicine in adults, and even in those studies which do demonstrate a statistically significant benefit in adults, the benefit was found to be small [3]. There are risks of interaction with other medicines leadings to serotonin syndrome. Cases of abuse and dependence have been reported [13].

Table 2: Non-pharmacological options for dry coughs (list not exhaustive)

Treatment	**Examples**	**Evidence of efficacy and other considerations**
Honey	Mixed with warm water, lozenges	A meta-analysis showed that honey (any formulation) was superior to usual care for the improvement of symptoms of upper respiratory tract infections, particularly cough frequency and cough severity. The term 'usual care' in this analysis grouped any commonly used treatments which included diphenhydramine, dextromethorphan, antibiotics, chlorphenamine and guaifenesin [14]. Comparisons with placebo are more limited (2 studies). More high quality, placebo controlled trials are required [14]. A Cochrane systematic review found that for children, honey probably relieves cough symptoms to a greater extent than no treatment,

		diphenhydramine and placebo. There may be little to no difference compared to dextromethorphan suggesting that honey may have a similar effect as dextromethorphan in reducing cough frequency [15]. Honey is not recommended in children under the 12 months due to the risk of botulism.
Demulcents	Glycerol syrup	Glycerol can be found in many cough syrups. It may be a major component for the efficacy of the cough syrup despite it being added as a thickening agent or solvent. Up to 85% of the benefit of cough syrups may be due to the physical and chemical effects of the glycerol from its demulcent action in the pharynx, coating and lubricating the pharyngeal surface. The moisturising properties of glycerol may also help to soothe inflamed mucosal surfaces in the pharynx [16]. Lemsip Dry Cough syrup is a General Sale medicine containing glycerol. The direction on the package states it can be used in children and adults 6 years and older. There is currently no published research on the efficacy of glycerol as a cough treatment [16].

Comment:
Sedating antihistamines are used as the cough suppressant component of many compounded cough preparations available over-the-counter. They all tend to cause drowsiness which may reflect their main mode of action [7].

Persistent cough

People who report a persistent cough lasting greater than 4 weeks should be advised to see their general practitioner [17]. A comprehensive history, good examination and appropriate investigations will identify the cause in the majority of people with a chronic cough. Investigating the underlying cause and directing therapy to eliminate the aetiology rather than to use empirical non-specific cough medicine is important for people presenting with persistent dry cough [18].

2.4 Anaphylaxis to neuromuscular blocking agents

2.4.1 Mechanism of IgE-medicated allergy

Anaphylaxis is a life-threatening, systemic immediate hypersensitivity reaction to an allergen. Symptoms typically occur within 30 minutes of exposure (usually within 5 minutes). Classic anaphylaxis results from IgE-mediated mast cell and basophil degranulation releasing histamine and other mediators. Non IgE-mediated reactions (previously referred to as "anaphylactoid") are clinically identical but are induced by direct interaction of the allergen with the mast cells or basophils [19].

The IgE-mediated reaction occurs after exposure to an antigen (allergen) that stimulates the production of IgE antibodies by B cells. After the initial exposure, antibody concentrations decease, but allergen-specific IgE binds to high-affinity IgE (Fc-epsilon-RI) receptors on mast cells and basophils. If there is a subsequent exposure to the antigen, it interacts with any surface-bound IgE that is specific for that allergen. Certain allergens are able to interact with IgE molecules on 2 or more receptors of the cell surface to cause cross-linking, which in turn causes the receptors to become aggregated and initiate intracellular signalling. Allergens that are capable of cross-linking are either multivalent (having multiple identical sites for IgE antibody binding) or univalent (having multiple different sites for IgE antibody binding). If signalling is sufficiently robust, the mast cell (or basophil) becomes activated and degranulates, releasing preformed mediators, enzymes, and cytokines (such as histamine, tryptase, and tumor necrosis factor [TNF], respectively) and initiating additional mediator, cytokine, and enzyme production. These mediators either act directly on tissues to cause allergic

symptoms or recruit and activate additional inflammatory cells, particularly eosinophils. The recruited cells, in turn, release more mediators and propagate a fulminant "chain reaction" of allergic inflammation [19].

IgE mediated anaphylaxis represent approximately 60 percent of perioperative anaphylaxis [1].

2.4.2 Incidence of anaphylaxis to NMBAs

The Royal College of Anaesthetists 6th National Audit Project on perioperative anaphylaxis in the United Kingdom reported that the overall incidence of NMBA-induced anaphylaxis was 5.3 per 100,000 exposures. Succinylcholine (suxamethonium) had the highest incidence (11.1 per 100,000 exposures) [20]. A total of 266 cases of intraoperative anaphylaxis were reported over a one-year period (2016) from all NHS hospitals in the UK. In 64 (25%) of these, the trigger was identified as a NMBA, including rocuronium (42%), atracurium (35%), succinylcholine (22%) and mivacurium (1.5%) [20] – see Table 3 .

Table 3: Neuromuscular blocking agents confirmed as causative agents by the review panel: absolute and relative risk [20].

[redacted]

The incidence of anaphylaxis to NMBAs varies between countries. In 2000, the Norwegian Medicines Agency (Statens Legemiddelverk) issued a recommendation to Norwegian anaesthetists to stop using rocuronium in routine anaesthetic practice. The Agency had received 29 reports of anaphylaxis or anaphylactoid reactions to rocuronium over a two-and-a-half-year period in which approximately 150,000 patients had received the medicine. This number was significantly higher than in other Nordic countries, where a total of only seven cases of anaphylaxis had been recorded in approximately 800,000 patients administered rocuronium up to December 2000 (Table 4) [19].

Table 4: Number of patients exposed to rocuronium, associated cases of anaphylaxis and derived incidence rate of anaphylaxis in the Nordic countries [21]

[redacted]

Although the reason for this discrepancy between Nordic countries was unclear, the apparent increase in anaphylactic reactions with rocuronium use in Norway was postulated to be due to differences in the reporting of anaphylaxis to NMBAs, and to statistical and methodological problems associated with rare adverse events (such as small sample size, skewed distribution of data and statistical variance). Marginal under-reporting has a disproportionately large effect on calculated incidence when the event being recorded occurs only very rarely [19].

In 2003, Mertes et al reported the results of a 2-year survey (January 1, 1999, and December 31, 2000) of anaphylactic (IgE mediated) or anaphylactoid (non-IgE mediated) reactions occurring during anaesthesia in France. NMBAs were the most common cause of anaphylaxis (306/789, 58.2%), with rocuronium (43.1%) and succinylcholine (22.6%) the most frequently incriminated [22].

In 2011, the same authors reported on an 8-year survey of anaphylaxis during anaesthesia in France from 1 January 1997 to 31 December 2004. Estimated incidence was obtained by combining survey data with data from the French pharmacovigilance system. Exposure data was obtained from data collected during a national survey of anaesthesia practice. A NMBA was the most common cause of IgE mediated reactions, occurring in 1067 of 1816 cases (58.8%). A diagnosis of IgE-mediated reaction was established in 72.18% of the cases [19].

The incidence of IgE mediated anaphylaxis in Western Australia was estimated to be 2.8 and 8.0 per 100,000 exposures for vecuronium and rocuronium, respectively. Rocuronium was responsible for 56% of cases of NMBA anaphylaxis, succinylcholine 21%, and vecuronium 11% [19].

In the 2012-2014 Triennial Report of the Victorian Consultative Council on Anaesthetic Mortality and Morbidity there were four deaths due to anaphylaxis (two suxamethonium, two rocuronium) and a total of 48 cases of anaphylaxis causing morbidity. More than half (25 case reports) were due to the administration of NMBAs, 13 cases were due to antibiotics and 10 due to other adjuvant agents [19].

Brusch et al compared reported rates of anaesthetic-associated anaphylaxis in various countries and regions (Table 5) and noted that NMBAs account for 11% of anaesthesia-related reactions in the United States, compared to approximately 60% in Europe and Australia [19].

Table 5: Reported rates of anaesthetic-associated anaphylaxis by country/geographical region

[redacted]

An Auckland observational study by Reddy et al showed that during a 7-year period, 92,858 new patients were exposed to NMBAs. During this period 21 patients were diagnosed with NMBA-related anaphylaxis. The incidence of perioperative anaphylaxis from various NMBAs is outlined in Table 6. The principal finding of this study was that use of succinylcholine (suxamethonium) and rocuronium was associated with a substantially higher rate (10-fold higher) of perioperative anaphylaxis compared with atracurium and other NMBAs (vecuronium, pancuronium and mivacurium) [23].

There was similarity between the incidence of anaphylaxis to rocuronium and succinylcholine (approximately 1:2,500 and 1:2,000, respectively). In contrast, the rate of anaphylaxis to atracurium was substantially lower (1:22,000). There were no cases of anaphylaxis from vecuronium in this dataset with an exposure of 9,585 people. [23].

Table 6: Intraoperative Incidence of Neuromuscular-blocking Drug-related anaphylaxis in Auckland, New Zealand

[redacted]

The authors commented that the data are limited to the Auckland region. Extrapolation to other regions need to be done with caution as geographical differences in sensitivity to NMBAs are likely, and may be based on regional differences in exposure to other sensitising agents.

Comments:

In this Auckland study, suxamethonium and rocuronium was associated with a 10-fold higher rate of perioperative anaphylaxis compared with atracurium, vecuronium, pancuronium and mivacurium. Events of anaphylaxis may not be observed for vecuronium, pancuronium and mivacurium due to their considerably lower usage. There appears to be different risk of anaphylaxis among the NMBAs in New Zealand and internationally.

2.4.3 NMBAs used New Zealand

NMBAs may be non-depolarising or depolarising [24].

Non-depolarising NMBAs competes with acetylcholine for receptor sites at the neuromuscular junction. This group can be divided into 2 structural classes: aminosteroid (pancuronium, rocuronium and vecuronium) or benzylisoquinolinium (atracurium and mivacurium) [24].

Depolarising NMBAs (eg, suxamethonium) act by mimicking acetylcholine at the neuromuscular junction [24].

The above mentioned NMBAs are funded on the Hospital Medicines List.

NMBAs differ in their onset of effect, duration of action, and adverse effects.

The class of NMBAs used for achieving neuromuscular blockade must be selected carefully based on patient factors, the type of procedure being performed, and clinical indication (Table 7) [25].

Example of factors to consider when selecting a NMBA for a particular procedure (eg, rapid sequence intubation (RSI)) is outlined below [26, 27]:

- Depolarising NMBAs (eg, suxamethonium) have a faster onset than non-depolarising NMBAs and are often chosen for RSI. Rocuronium has the fastest onset of all non-depolarising NBMAs and therefore may be used at higher doses as an alternative to suxamethonium.
- Vecuronium and pancuronium are alternatives for RSI, but have fallen out of favour because of the slower onset time compared to rocuronium.
- Mivacurium was developed as a non-depolarising alternative to suxamethonium. Large doses are required for intubation due to its low potency. Its use is limited due to the histamine release profile.
- Pancuronium is rarely used because of a high incidence of postoperative residual neuromuscular weakness.

Table 7: Characteristics and considerations of different NMBAs [24, 25, 27, 28]

	NMBA	Onset of effect (minutes)	Duration (minutes)	Considerations
Short-acting	Suxamethonium	0.5-1.5	5-10	Histamine release: minimal Hyperkalaemia Cardiovascular reactions Ideal for use when fast onset and brief duration of action is required (eg, tracheal intubation)
	Mivacurium	2-3	10-20	Histamine release: low to minimal Cardiovascular reactions

				Metabolism via plasma cholinesterase therefore patient deficient in this enzyme may have prolonged muscle paralysis
Immediate-acting	Atracurium	3-5	20-35	Histamine release: low to minimal Seizures reported in ICU patients receiving long-term atracurium infusion to support mechanical ventilation Cardiovascular reactions Metabolism independent on liver or kidney function
	Rocuronium	1-2	20-35	Histamine release: minimal to none Vagolytic and sympathomimetic effects can cause tachycardia and hypertension Excreted in urine and bile. Caution in renal and hepatic inpairment
	Vecuronium	3-5	20-45	Histamine release: none. Excreted in urine and bile. Caution in renal and hepatic inpairment
Long-acting	Pancuronium	2-5	60-100	Histamine release: minimal to none Cardiovascular reactions

Exposure to NBMAs in Auckland (covering Auckland and North Shore Hospitals) during a 7-year period is outlined in Table 8 [23].

Table 8: New patient exposure to a NMBA in Auckland between the years 2006 and 2012

NMBA	Number of patients exposed
Atracurium	67,354
Suxamethonium	24,960
Rocuronium	14,995
Vecuronium	9,585
Pancuronium	3,799
Mivacurium	1,658

Reports of NMBA-related anaphylaxis to CARM

Up to 15 May 2023, CARM had received 648 reports where a NMBA was listed as a suspect or interacting medicine in an anaphylactic reaction (using the MedDRA PTs anaphylactic reaction, anaphylactic shock and anaphylactoid reaction). The most reported NMBA was rocuronium (331 reports). This was followed by suxamethonium (230 reports), atracurium (54 reports), vecuronium (34 reports), mivacurium (12 reports) and pancuronium (6 reports). Rates cannot be estimated due to spontaneous reporting and the absence of a denominator.

2.4.4 Role of quaternary ammonium ion (QAI) in NMBA-related anaphylaxis

The molecular basis of anaphylaxis to NMBAs is recognition by IgE antibodies of tertiary or quaternary ammonium ions (QAI) present on all NMBAs, which also accounts for the allergenic cross-reactivity seen between NMBAs (Figure 2). The antibodies do not recognise primary and secondary amino groups. All NMBAs have at least two tertiary and/or quaternary ammonium ions. The distance between the ammonium ions is sufficient to bridge adjacent mast cell-bound IgE molecules, thereby inducing mast cell mediator release.

Other amines, including tertiary structures have also been shown to function as haptens and to inhibit the QAI-specific reaction [19].

Currently-used NMBAs are either mono-quaternary (vecuronium and rocuronium) or bisquaternary (suxamethonium, atracurium, mivacurium, pancuronium). There is no evidence that the risk of anaphylaxis is related to the number of quaternary ammonium groups. Individuals may be allergic to more than one NMBA. Cross-sensitivity (based on skin testing and specific IgE) is common, with suxamethonium being the most commonly cross-reacting drug. Cross-sensitivity may occur between different classes of NMBA as well as within classes [19].

Figure 2: Molecular structures of pholcodine, morphine, suxamethonium and rocuronium [19]

The majority of patients who experience anaphylaxis to a NMBA have not had prior exposure to any drug of this class. As prior exposure is a prerequisite for IgE-mediated anaphylaxis, these patients must have been exposed to a molecule with cross-reactivity to the allergenic component of the NMBA [19].

Since compounds containing tertiary and/or quaternary ammonium groups occur widely in the human environment, for example in medicines, cosmetics, disinfectants, industrial materials and food, it has been suggested that sensitisation to NMBAs may occur via these sources and this could explain the lack of previous exposure seen in many of the anaphylactic patients [19].

There has also been significant interest in whether pholcodine consumption causes production of specific IgE against QAI over the last 10-15 years. Ecological studies suggested a link between prior pholcodine consumption and an increased risk of anaphylaxis with NMBAs. Studies have shown that in areas without ongoing pholcodine consumption, IgE antibodies to pholcodine and suxamethonium falls. Re-exposure has a profound booster effect and there is a dramatic rise in pholcodine antibodies in individuals with known previous sensitisation to pholcodine and suxamethonium. Pholcodine was withdrawn from the Norwegian market in 2007. Three years after withdrawal, the rate of anaphylactic reactions to NMBAs in Norway were reported to have significantly reduced [29]. Please refer to Annex 1 for a summary of the ecological association.

2.5 Product prescribing and labelling information

2.5.1 New Zealand data sheet

Section 4 of the Duro-Tuss Liquid Regular 15mg/15mL (from iNova Pharmaceuticals) data sheet is presented in Table 9 [2].

Table 9: Section 4 of the Duro-Tuss Liquid Regular 15mg/15mL data sheet

Section	Wording
Dose and method of administration	Based on 15mg/15mL strength <table><tr><th>Age</th><th>Dosage</th><th>How often</th></tr><tr><td>Adults & children 12 years & over</td><td>10 – 15 mL</td><td rowspan="3">Every 6 hours as required (Maximum 4 times a day)</td></tr><tr><td>Children 6-11 years</td><td>5 – 10 mL</td></tr><tr><td>Children under 6 years</td><td>Do not use</td></tr></table>
Contraindications	Children under the age of 6 years. Hypersensitivity to pholcodine or any of the excipients listed in section 6.1. Patients in, or at risk of developing respiratory failure, (may depress respiration). Patients with chronic bronchitis, COPD, bronchiolitis or bronchiectasis due to sputum retention. Patients with renal or hepatic failure. Patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such treatment (see also section 4.5).
Special warnings and precautions for use	Use with caution in patients with liver or renal disease. Pholcodine should be used with caution in patients with chronic or persistent cough, asthma including an acute asthma attack or where cough is accompanied by excessive secretions. Severe cutaneous adverse reactions (SCARs) including acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in patients treated with pholcodine-containing products, most likely in the first week. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Duro-Tuss Dry Cough Liquid Regular should be withdrawn immediately. Concomitant use of Duro-Tuss Dry Cough Liquid Regular with other medicines intended to treat the symptoms of the common cold is not recommended. **Cross-reactivity leading to serious allergic reactions (anaphylaxis) have been reported between pholcodine and Neuromuscular Blocking Agents (NMBAs). A precise at-risk period of time between the exposures of pholcodine and NMBAs has not been determined. Clinicians should be aware of this potential in case of future anaesthetic procedures involving NMBAs.** Use of pholcodine with alcohol or other central nervous system (CNS) depressants may increase the effects on the CNS and cause toxicity in relatively smaller doses. This product contains sorbitol which may have a laxative effect or cause diarrhoea in some people.
Interaction with other medicines	Do not use in patients taking MAOIs or within 14 days of stopping treatment. **Interaction with neuromuscular blocking agents (anaphylaxis) has been reported (see Section 4.4).** The reduction in blood pressure caused by antihypertensives may accentuate the hypotensive effects of pholcodine. Diuretics may have the same effect. Pholcodine may enhance the sedative effect of CNS depressants including alcohol, barbiturates, hypnotics, narcotic analgesics, sedatives and tranquillisers (phenothiazines and tricyclic antidepressants).
Fertility, pregnancy and lactation	Category A The safety of pholcodine during pregnancy and lactation has not been established. Based on the available data for morphine, it would seem likely that use of pholcodine during pregnancy would not be associated with congenital defects and that use of pholcodine during lactation would not be contraindicated. However, its use should be carefully assessed by consideration of small benefits versus potential risk to the foetus or neonate.

Effects on ability to drive and use machines	This medicine can impair cognitive function and can affect a patient's ability to drive safely or operate machinery. Patients should therefore exercise caution before driving or use of machinery until they know DuroTuss Dry Cough Liquid Regular does not adversely affect their performance.
Undesirable effects	The following side effects may be associated with the use of pholcodine: Occasional drowsiness, dizziness, excitation, confusion, sputum retention, vomiting, gastrointestinal disturbances (nausea and constipation). Skin and subcutaneous tissue disorders: Skin reactions including rash. Acute generalized exanthematous pustulosis (see section 4.4) (frequency unknown) Immune system disorders have been noted including hypersensitivity reactions and anaphylaxis.
Overdose	Pholcodine is thought to be of low toxicity, but the effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs. Symptoms: These include nausea, drowsiness, restlessness, excitement, ataxia and respiratory depression. Management: Treatment of overdose should be symptomatic and supportive. Gastric lavage may be of use. In cases of severe poisoning the specific narcotic antagonist nalaxone may be used. Information for children: Nalaxone has been used successfully to reverse central or peripheral opioid effects in children (0.01mg/kg body weight). Another treatment option is activated charcoal (1g/kg body weight) if more than 4mg/kg has been ingested within 1 hour, provided the airway can be protected.

Comments:

Section 4.4 (special warnings and precautions for use) of the data sheet has information on pholcodine-NMBA sensitisation and advises clinicians to be aware of this potential in case of future anaesthetic procedures involving NMBAs.

2.6 Usage

[redacted]

[redacted]

3 REVIEW OF THE EFFICACY AND SAFETY OF PHOLCODINE

3.1 Literature review

Much of the available information has previously been reviewed in the benefit-risk review prepared for the December 2019 MARC meeting. Please refer to Annex 1.

An updated literature search was conducted to identify newer publications on the efficacy and safety of pholcodine. Relevant literature not considered in the previous report is also included below.

3.1.1 Literature update – efficacy

No recent efficacy studies were identified.

3.1.2 Literature update – safety

Six case reports that describe the safety of pholcodine were retrieved (Table 12)

Table 12: Case reports in the literature describing the safety of pholcodine

Author and reference #	Case report narrative
Esnault et al [30]	A 52-year-old male with a history of hypertension and dyslipidaemia ingested 750 mg of pholcodine syrup in 2 hours. An hour after the last bottle, he felt uncomfortable and complained of dyspnoea. He was later found to be to be in a non-shockable cardiac arrest. Toxicology analysis showed pholcodine blood levels of 2,500 ng/ml (a lethal dose is >1,000 ng/ml, extrapolated from animal studies). The authors hypothesise that cardiac arrest was the result of hypoxia due to respiratory arrest connected to the opioid nature of pholcodine.
Kline et al [31]	A 11-year-old female consumed Duro-Tuss Dry Cough Liquid Regular (containing pholcodine) and developed a pruritic, erythematous rash over her right flank, with pustules developing over the following 48 hours. The rash became more extensive. Over the following 2 days, the rash evolved to a generalised, erythematous eruption with occasional pustulation. The patient became febrile to > 39°C on multiple occasions. She was very unwell and not able to walk. Her white blood cell count increased to 37.9 × 10^9/L, with a marked neutrophilia. Histology supported a drug eruption and due to the clinical presence of pustulation, marked neutrophilia and negative microbiological investigations, acute generalised exanthematous pustulosis (AGEP) secondary to pholcodine was diagnosed.
Acker et al [32]	A 47-year-old female presented with an erythematous, papular and itchy dermatitis accompanied by general malaise and fever. The skin eruption started on her legs but rapidly generalised to an erythroderma requiring hospitalisation. Pholcodine was used in the last 36 hours. The patient was diagnosed with severe cutaneous adverse reaction to pholcodine.
Codreanu et al [33]	A 33-year-old female presented with facial angioedema 8 hours after taking a syrup containing pholcodine with domperidone, tixocortol and bacitracine for a sore throat. She had a history of facial angioedema related to beta-lactam. Intradermal test to pholcodine was positive while negative for the other medicines. An oral rechallenge with pholcodine was positive showing laryngeal angioedema 9 hours after the second dose and disappearing a few hours after corticosteroid injection.
Epain et al [34]	This case series describes 3 fatalities following pholcodine intoxication.

	Case 1: a 50-year-old female was found unconscious in the bedroom. Her death was attributed to acute pholcodine intoxication. She had major comorbidities which may also have played a role. Case 2: a 46-year-old female was found unconscious and breathing raucously at home. The cause of death was declared to be fatal acute pholcodine intoxication, with cardiac status as a possible contributory factor. Case 3: a 21-year-old female was found dead at home. Death was attributed to acute pholcodine intoxication. Macroscopic and histologic examination found no acute lesions or chronic illness that could explain the death. She had other health conditions that may have played a role. The first and third cases had morphine detected in urine and blood. The presence of morphine may have resulted from minor pholcodine metabolism pathway, although intake of morphine or heroin could not be formally excluded for these cases. Toxicological hair analyses were performed to investigate history of pholcodine consumption. In one case, occasional use was disclosed, in line with prescription recommendations for symptomatic treatment of unproductive cough. For the other two cases, although interpretation is hindered by a lack of published date, the pholcodine concentrations in hair seemed to indicate repeated and escalating use of medicine during the months preceding death, constituting if not abuse at least misuse of this medicine. The authors concluded that pholcodine can be involved in fatal poisoning and raises the question of misuse or abuse.
Bulat et al [35]	A 23-year-old female developed Stevens-Johnson syndrome following pholcodine consumption. She also had COVID-19 at the time for which she received pholcodine for 11 days for dry cough. Three days after discontinuing pholcodine she developed erosive lesions in the oral cavity, with dysphagia and burning sensation. Concomitantly with the appearance of oral lesions, she noticed a rapid symmetrical development of erythematous macules with central dusky violaceous region on her thorax, which spread to her face, genital area, lower extremities, palms and soles. Her lesions healed without scarring 10 days after discontinuing pholcodine therapy.

Comments:

The updated literature search did not identify any new studies supporting the efficacy of pholcodine which is to be expected given the age of the product. Cases reporting adverse reactions to pholcodine were mainly dermatological reactions or fatal intoxication from pholcodine overdose.

3.1.3 Literature update – on pholcodine exposure and subsequent risk of NMBA-related anaphylaxis

3.1.3.1 Mertes et al 2023. Pholcodine exposure increases the risk of perioperative anaphylaxis to neuromuscular blocking agents: the ALPHO case-control study [36]

Aim: The ALPHO study was a multicentre case-control study investigating the relationship between prior pholcodine consumption within the last 12 months and the onset of perioperative anaphylaxis with a NMBA during general anaesthesia.

The secondary objective focused on the diagnostic value of specific IgE (sIgE) to quaternary ammonium (QA) and pholcodine for the prediction of perioperative anaphylaxis.

Methods: Patients who experienced perioperative anaphylaxis with a NMBA were assigned as cases. Controls were patients who had an uneventful anaesthesia with a NMBA. A case was matched with 2 controls based on the following:

- Age (more than and under 65 years of age)
- Sex
- Type of NMBA
- Geographical area (northern or southern France)
- Anaesthesia period corresponding to the date or reaction ± 90 days.

Cases underwent NMBA allergy skin testing (prick and intradermal). A centralised retrospective confirmation of NMBA-related cases was performed. Cases were excluded if they did not have at least one positive skin test for one of the NMBAs.

Controls were included by an anaesthetist investigator during their hospital stay. Controls were excluded if they had a history of perioperative anaphylaxis during anaesthesia or pregnancy at the time of screening. Controls were required to complete a medication self-administered questionnaire.

Data collected included medical history, drugs administered during anaesthesia, characteristics and management of the reaction, and occupation/profession. Patients reporting current or past cleaning profession or hairdressers were considered professionally exposed to QAs.

To ascertain previous exposure to pholcodine in the last 12 months, cases and controls completed a self-administered questionnaire. This had name and package visuals of currently available pholcodine products in France. Decoy products were also included. The second method for collecting past pholcodine exposure was through the patient's pharmaceutical history, retrieved by the participants from community pharmacy records (pholcodine containing medicines are prescription-only in France).

Concentrations of sIgE to pholcodine, sIgE to quaternary ammoniums and total IgE were analysed in both cases and controls using 2 assay techniques.

Results:

Patient characteristics:

167 cases were matched with 334 controls. Table 13 outlines the patient characteristics. Cases had a higher BMI and a significantly higher proportion of subjects were cleaners, had atopy, and had been exposed to pholcodine compared to controls ($p<0.01$).

Table 13: Characteristics of control and case and control cohorts

NMBAs involved in anaphylaxis:

An allergy work up was performed following NMBA-related anaphylaxis. Suxamethonium was incriminated in 101 (60%) cases, rocuronium in 21 (13%) cases, atracurium in 35 (21%) cases, cisatracurium in 11 (7%) cases, and mivacurium in two (1%) cases.

Multi-variate analysis:

The primary results showed a statistically significant link between use of pholcodine during the 12 months preceding anaesthesia and risk of perioperative anaphylactic reaction related to NMBAs (odds ratio (OR)= 4.2, 95% CI 2.5 to 7.0) (Table 14).

Professional exposure to quaternary ammonium compounds (OR= 6.1, 95% CI 2.7 to 13.6) were also associated with the risk of perioperative anaphylaxis to a NMBA. This suggests that apart from pholcodine, other environmental factors can also lead to sensitisation to NMBAs.

Lastly, hepato-gastrointestinal history was significantly associated with NMBA-related anaphylaxis.

Table 14: Risk factors for neuromuscular blocking agent-related perioperative anaphylaxis

An analysis was performed to determine whether different sources of information to ascertain pholcodine consumption had an effect on the ORs. The significant association between pholcodine consumption and NMBA-related anaphylaxis persisted when restricting the source of prior pholcodine exposure to self-questionnaire, when restricting to pharmacist-reported medication history, or when exposure was corroborated by the two sources. However due to small number of cases, the confidence interval was considered wide indicating less precision and an underpowered study.

Specific IgEs:

IgE to quaternary ammoniums: QA-SAQ sIgE was assayed in 160 (96%) cases and 334 (100%) controls, and QA-c260 in 162 (97%) cases and 333 controls.

IgE to pholcodine: pholcodine-SAQ sIgE was assayed in 160 (96%) cases and 334 (100%) controls and PHO-c261 in 162 (97%) cases and 333 controls.

Table 15 outlines the results of the sIgE assays in cases and controls. sIgE to pholcodine and QA had a high negative predictive value of 99.9% but a very low positive predictive value.

Table 15: Specific IgE levels in case and control cohorts from the ALPHO study and their respective diagnostic values.

[redacted]

There was no difference for sIgE values in cases and controls who reported using pholcodine in the previous year and those who did not, with the exception of PHO-c261 in controls (Figure 3).

Figure 3: Specific IgE (sIgE) level (in kUa/L) in cases and controls according to their pholcodine (PHO) consumption in the past year.

[redacted]

The authors state that this study demonstrated that patients exposed to pholcodine 12 months before exposure to an NMBA have a significantly higher risk of NMBA-related anaphylaxis. This strong association is observed regardless of the source used to estimate pholcodine exposure.

The results also suggest that other unidentified compounds containing tertiary ammonium ions or QA groups act as sensitising agents. These agents are widely present in the human environment among drugs, cosmetics, disinfectants, industrial materials and foods.

Results of sIgEs to pholcodine and QA showed excellent performance in discriminating cases from controls. This supports the recognition of common epitopes between the QA and pholcodine-sIgE tests.

sIgE to QA and pholcodine had an excellent negative predictive value supporting a low risk of NMBA-related anaphylaxis when their serum levels are undetectable. This could theoretically help to rule out the risk of NMBA-related anaphylaxis in patients reporting recent exposure to pholcodine within 12 months. Conversely, the low positive predictive values of sIgE to QA and pholcodine suggests these markers would not be able to identify a population at risk of NMBA-related anaphylaxis with sufficient precision.

The limitations to this study include the methodology ascertaining prior pholcodine exposure. Although 2 imperfect, but complimentary sources were used there were observed higher proportion of missing information from controls, possibly due to the weaker motivation in the group to collect the required information from their pharmacist. There were also positive answers in the self-questionnaire not confirmed by the medication history of pharmacists. This may be due to patients using pholcodine products already available at home, possibly dispensed for other family member or someone else could have given it to them.

Conclusions:

The authors conclude that this study confirms a significant association between pholcodine consumption in the year preceding NMBA exposure and NMBA-related perioperative anaphylaxis. Other environmental factors, including occupational exposure to quaternary ammonium compounds, should be considered in the risk of NMBA-related anaphylaxis, but they currently remain poorly defined. In this context, pholcodine appears to be a well-identified risk factor that can be addressed.

Comments:

Accurately establishing pholcodine consumption is a limitation of this study but also reflects the 'real world' situation where patients may not always recall whether they have consumed a cough mixture or that it contained pholcodine. Despite this limitation, pholcodine exposure and NMBA-anaphylaxis was found to be significant when restricting the analysis based on separate source type and when the source types corroborated.

The low positive predictive value of sIgEs could not be used to establish a potential test to screen for people at risk of NMBA-related anaphylaxis with prior pholcodine exposure. In addition, testing may not be practical in many clinical settings such as in emergency situations where the use of NMBAs may be required urgently. However, it is not clear from the methodology whether testing sIgE levels was done prior to surgery or after the patient had received NMBA. If testing was performed after NMBA administration, the question remains on whether pholcodine or NMBA caused the raised sIgEs.

Some limitations of this study include: the low matching of 1 case to 2 controls and the unrefined matching criteria (eg, age and region in France).

3.1.3.2 Malvik 2022 et al. Gender-specific decline in perioperative allergic reactions in Norway after withdrawal of pholcodine [Letter to the Editor] [37]

Aim: To investigate the influence of gender on the decline in perioperative hypersensitivity reports following withdrawal of pholcodine in Norway in 2007.

1,379 reports from 1997 to 2017 were analysed based on standardised reports of patient characteristics, clinical presentation, and laboratory investigations.

Results: Of the 1,379 reported cases, 461 were men and 918 were women. The median age was 42 years (range 0–89 years). Muscle relaxants were used in 1,023 patients (74.2%). There was a female predominance in all age-groups.

There was no clinically relevant gender difference in the increase in serum tryptase for the different grades of anaphylaxis severity.

From 1997 to 2007, on average 76 cases of suspected NMBA hypersensitivity reactions were reported per year. Following the withdrawal of pholcodine in 2007, reports fell to 61 per year, with stable reporting from 2009.

The gender difference was significant in both periods of stable reporting. From 2001 to 2007, there was a 72% female predominance ($p<0.01$), and from 2009 to 2017, 60% were women ($p<0.01$) (Figure 4).

Figure 4: Temporal trends in a number of reports of suspected perioperative hypersensitivity reactions from 1997 to 2017, grouped by gender. Continuous line constructed using locally weighted scatterplot smoothing, and transparent area equals standard error.

Discussion and conclusions: A decline in number of reports of NMBA-related hypersensitivity was observed following the withdrawal of pholcodine in Norway in 2007. Most of this reduction had taken place among women. If this gender-specific decline in reports is attributable to the withdrawal of pholcodine, a possible explanation could be differences in patterns of consumption between men and women. However, there is no information about the pattern of use by gender.

There was no gender difference in total IgE or in absolute or relative tryptase levels. No difference in the clinical severity of the reaction between gender were seen and this is in line with similar biochemical findings.

Women are overrepresented in the database of the Norwegian Network for Anaphylaxis under anaesthesia, accounting for two thirds of reported cases. After the withdrawal of pholcodine from the Norwegian market, the gender difference has become less pronounced.

3.1.3.3 Sadleir et al 2021. Relationship of perioperative anaphylaxis to neuromuscular blocking agents, obesity, and pholcodine consumption: a case-control study [38]

Aim: Patients anaesthetised for bariatric surgery appear to have a higher than expected risk of perioperative anaphylaxis in Western Australia. The aim of this Western Australian case-control study was to test the hypothesis that obesity is a risk factor for NMBA-related anaphylaxis, independent of differences in pholcodine consumption.

The authors also sought to estimate the risk of NMBA-related anaphylaxis in patients presenting for bariatric surgery in Western Australia compared with the risk in the overall surgical population and the relative risk

of rocuronium anaphylaxis compared with vecuronium anaphylaxis, using controls as an approximation of market share.

Methods: A blinded case-control design compared a group of patients with anaphylaxis to NMBAs (cases) to a group of patients who had anaphylaxis to cefazolin and also received a NMBA prior to the anaphylactic event (controls) with respects to BMI grade, history of pholcodine consumption within the last 12 months, sex, comorbid disease and NMBA type and dose.

Confounding was assessed by stratification and binomial logistic regression.

The source population was patients referred to an anaesthesia allergy clinic between 2012 to 2020 for investigation of suspected intraoperative anaphylaxis. Historical cases and controls were collected from 2012 and 2016, and concurrent cases and controls from 2016 to 2020.

The patient's anaesthetic record, allergy clinic referral letter, standardised assessment notes, skin testing results and investigations, and allergist reply correspondence were reviewed for all participants. For historical cases and controls, patients were contacted and interviewed if their records did not explicitly record pholcodine exposure. All concurrent cases had pholcodine consumption determined before skin testing (blinded).

Pholcodine consumption was classified as 'definite', 'uncertain', or 'absent'.

- 'Definite' pholcodine consumption required patient confirmation using a picture of the pharmaceutical packaging for the consumed preparation.
- 'Absent' consumption was defined as no history of use of cough medicines or consumption of a cough medicine that was identified as not containing pholcodine.
- 'Uncertain' consumption was defined as possible or certain consumption of a cough suppressant, but which could not be identified sufficiently to determine whether or not it contained pholcodine.

Results: 145 cases and 61 controls were included in the final analysis. Characteristics of patients are outlined in Table 15.

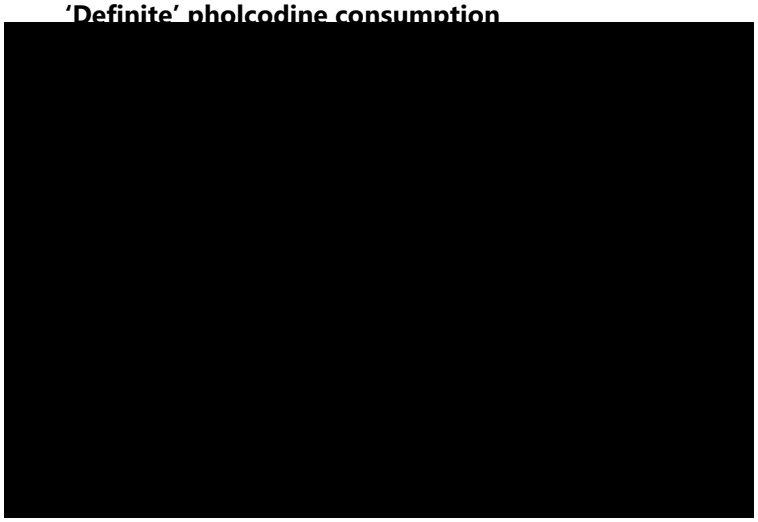
Table 16: Characteristics of participants and univariate analysis of exposure variables

Obesity (BMI >29.9 kg/m^2) (odds ratio [OR]=2.96, 95% CI 1.57 to 5.58, p=0.001), 'definite' pholcodine consumption (OR=14.0, 95% CI 4.2 to 46.9, p<0.001), and female sex (OR=2.70, 95% CI 1.42 to 46.9, p=0.002) were statistically significant risk factors for NMBA-related anaphylaxis on univariate analysis.

The risk of NMBA-related anaphylaxis also increased with BMI grade. This dose-response persisted in patients who did not have a history of 'definitive' pholcodine exposure, suggesting obesity was associated with NMBA-related anaphylaxis independent of pholcodine consumption.

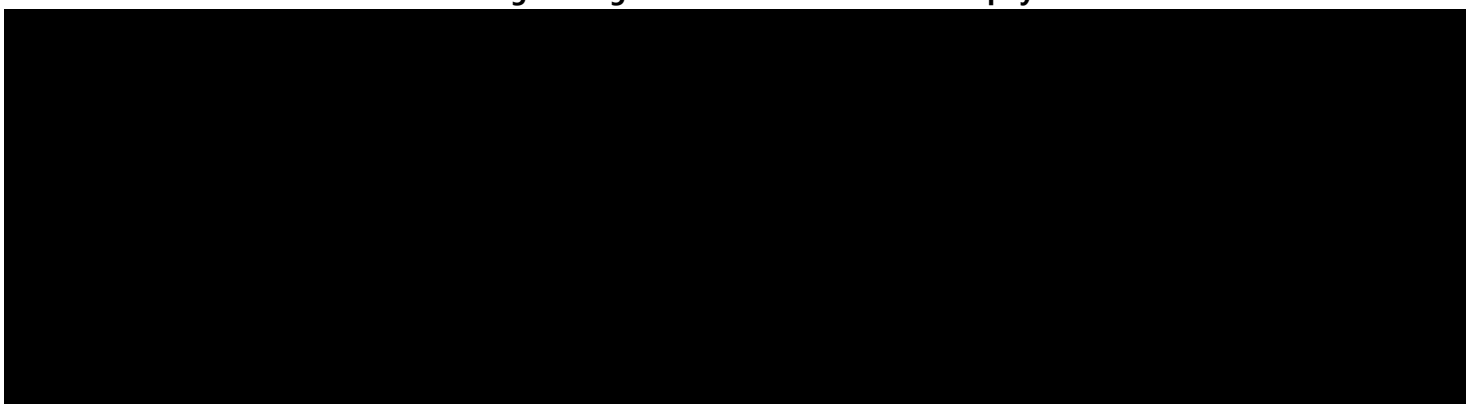
Pholcodine consumption 12 months prior to surgery was an independent risk factor for NMBA-related anaphylaxis: 'Definite' pholcodine consumption' dramatically increased the odds of NMBA-related anaphylaxis compared to 'no pholcodine consumption' (OR= 12.4, 95% CI 3.61 to 42.9, p=0.0001). There was no significant difference between 'uncertain' pholcodine consumption and 'no' pholcodine consumption in the odds of NMBA-related anaphylaxis (Figure 5).

Figure 5: Percentage of subjects with NMBA anaphylaxis in the categories of 'No', 'Uncertain' and 'Definite' pholcodine consumption



Confounding analysis indicated that both obesity and definitive pholcodine consumption remained important risk factors after correction for confounding. The patient's gender did not remain an important risk factor following correction (Table 16).

Table 17: Initial and final binomial logistic regression model for NMBA anaphylaxis



Rocuronium was administered to 73.3% of controls and was the responsible trigger in 73.8% of cases of NMBA anaphylaxis. The relative rate of rocuronium anaphylaxis was estimated to be 3.0 times that of vecuronium using controls as an estimate of market share, and the risk of NMBA anaphylaxis in patients presenting for bariatric surgery was 8.8 times the expected rate (74.9 vs 8.5 per 100 000 anaesthetic procedures).

Discussion on strengths and limitations:

The authors stated that the strength of this study included the restricted selection of controls which minimised confounding by indication for NMBAs. Both cases and controls were exposed to NMBAs which is usually reserved for patients with particular characteristics (such as unfasted, obese) or undergoing certain types of surgeries. Characteristics associated with the need for NMBA administration would therefore be expected to be equally distributed between groups.

Systematic errors were minimised by using a restricted control group that was indistinguishable from the case group at the time of data collection. Selection bias was minimised by choosing a homogeneous group of patients who all received an NMBA and had all suffered perioperative anaphylaxis.

The authors also state that recall bias was minimised by limiting the period of consumption to 12 months before the reaction, and by determining history of pholcodine consumption and BMI before skin testing in concurrent cases.

Conclusions:

Obesity is a risk factor for NMBA anaphylaxis, the risk increasing with BMI grade. Pholcodine consumption is also a risk factor, which is consistent with the pholcodine hypothesis. In Western Australia, rocuronium use is associated with an increased risk of anaphylaxis compared with vecuronium in this population.

There may be unidentified sensitisers other than pholcodine that exist in the community that obese patients are more likely to be exposed to.

Comments:
Similar to the ALPHO study, a limitation of this study was accurately establishing prior pholcodine consumption. This may potentially misclassify cases.
The ALPHO study showed the risk of anaphylaxis applies to any NMBA. In contrast, this study found that there was a higher rate of anaphylaxis following rocuronium compared to vecuronium. It may be possible that the risk factors measured are specific for rocuronium rather that general to all NMBAs, however more research is needed to determine this.

3.1.3.4 Anderson et al 2020. Measurement of pholcodine-specific IgE in addition to morphine-specific IgE improves investigation of neuromuscular blocking agent anaphylaxis [39]

Background: Specific IgE (sIgE) to NMBAs is frequently examined using morphine as a marker for the substituted ammonium groups. Pholcodine has also been suggested as an effective marker for detection of sIgE to substituted ammonium epitopes. There is considerable variation between sIgE concentrations to morphine or pholcodine in NMBA allergic patients.

This study investigated the variation and the value of using pholcodine sIgE assay in the assessment of NMBA allergic patients.

Methods: A retrospective study was carried out for all patients investigated at an Anaesthetic Allergy Clinic in Sydney, Australia from June 2009 to September 2019. Standardised skin testing was performed with a panel of NMBAs including rocuronium, vecuronium, pancuronium, succinylcholine (suxamethonium), and cisatracurium. Measurement of pholcodine and morphine sIgE was performed for all patients.

Results: A total of 801 consecutive patients were examined. Of these, 255 exhibited positive skin test results for NMBAs.

Pholcodine-sIgE concentrations were quantitatively higher than morphine-sIgE concentrations in 56% of skin test-positive patients with morphine-sIgE concentrations higher than pholcodine-sIgE in 24%. Where patients had pholcodine-sIgE concentrations two or more times the concentration of morphine-sIgE (ie, pholcodine/morphine sIgE ratio ≥2), a significantly increased proportion had skin sensitisation to succinylcholine (suxamethonium) compared to patients who had a pholcodine/morphine sIgE ratio ≤1. This difference was not seen with other NMBAs tested (Table 17).

Table 18: Comparison of pholcodine/morphine sIgE ratios for various neuromuscular blocking agent sensitivity.

Conclusions: Comparison of variation in the concentrations of sIgE to pholcodine and morphine may provide increased information regarding which NMBAs could present a risk for future procedures. The results from the current analysis suggest that this may be of use in the assessment of risk associated with subsequent succinylcholine (suxamethonium) exposure.

Comments:
In this study, over half of the patients who tested skin test positive for NMBA had quantitatively higher pholcodine-sIgE concentration than morphine-sIgE. However, 20% of patients had similar concentrations of pholcodine and morphine sIgE, suggesting there may be limited utility in measuring sIgEs to accurately assess patients who are allergic to NMBAs.

3.1.3.5 Case reports

Table 18 outlines case reports in the literature that describe pholcodine sensitisation to NMBAs

Table 19: Case reports in the literature describing pholcodine sensitisation to NBMAs

Author and reference #	Case report narrative
Touraine at al [40]	A man presented with dyspnoea, chest tightness and pruritus on the palms 30 minutes after taking pholcodine syrup (Biocalyptol) for a cough. He had not been previously exposed to NMBAs. He was subsequently re-exposed to pholcodine twice and developed hypersensitivity reactions. Allergy tests performed revealed positive prick tests for Biocalyptol and another pholcodine syrup [Respilene]. A prick test was positive for suxamethonium chloride and skin tests were positive for rocuronium bromide and pancuronium bromide. Specific IgE antibodies against QAI were very high. This observation showed sensitisation to NMBAs in a patient who presented a severe reaction to pholcodine without previous anaesthesia.
Fourel et al [41]	A 66-year-old female was referred for allergy testing following mucocutaneous oedema of the face after taking pholcodine. She previously had pholcodine in the past, but the oedema was relatively superficial. Skin prick test, intradermal test, and basophil activation test confirmed sensitisation to 3 NMBAs. The report highlights that prior exposure to NMBAs cannot be ruled out as she had 2 prior surgeries requiring general anaesthesia (anaesthetic used not known).
Petitpain et al [42]	The authors describe 4 patients with proven pholcodine sensitisation to NMBAs.

	The first case was a patient who experienced NMBA-related anaphylaxis. Two months prior they had a hypersensitivity spectrum reaction to pholcodine. Skin tests (prick and intradermal) confirmed pholcodine and suxamethonium allergy, with cross-reactivity to rocuronium and vecuronium. The other 3 cases were referred to hospital following pholcodine anaphylaxis. Allergy tests confirmed pholcodine allergy and revealed NMBA sensitisation, despite no history of NMBA anaphylaxis. Two of the cases had a positive basophil activation test for suxamethonium. Considering these results, NMBAs skin tests should be performed before anaesthesia in patients with confirmed pholcodine allergy.
Lee et al [43]	The authors describe two patients in Australia with pholcodine anaphylaxis who subsequently had positive skin tests to one or more NMBA. • A 76 year old female who was given pholcodine for a dry cough. Within 10 minutes of ingestion she developed facial pruritus, rash, hoarseness and tongue swelling. She had detectable specific IgE to pholcodine (7.14 kU/L) and morphine (1.91 kU/L) but not suxamethonium. NMBAs test showed a positive intra-dermal test to atracurium. Avoidance of pholcodine, cisatracurium and atracurium was advised. • A 40 year old female developed palmar itch, urticaria, facial oedema, throat tightness and syncope 20 minutes after ingesting a pholcodine-containing cough mixture and aspirin. Serum specific IgE was positive to morphine. Her intra-dermal test to suxamethonium was positive (a 9mm wheal). She was advised to avoid pholcodine and suxamethonium. Oral aspirin challenge is pending.
Horgan et al [44]	A 60-year-old lady reported developing urticaria on exposure to pholcodine. Investigations revealed a significantly elevated total IgE (24 206 kU/L) and very high specific IgE to pholcodine (37.2 kU/L). Further testing for cross-reactivity with NMBAs demonstrated a high specific IgE to rocuronium (>100 kU/L) and suxamethonium (19 kU/L). Intradermal testing to NMBAs revealed large wheals and flares for suxamethonium and rocuronium. The pancuronium, vecuronium, cisatracurium and atracurium intradermal tests were negative. The recommendations for future anaesthesia were to avoid NMBAs if possible. Atracurium was recommended as the safest alternative if an NMBA was absolutely necessary. The patient was also advised to avoid pholcodine. The authors retrospectively identified 7 cases of NMBA anaphylaxis at their hospital, of which five (71%) patients demonstrated a positive specific IgE to pholcodine, after the anaphylactic event. This raises the possibility that these patients were sensitised to NMBAs through prior pholcodine exposure.

Comments:

The majority of these case reports represent sensitisation to NMBAs following a prior hypersensitivity reaction to pholcodine.

3.2 Post-market spontaneous reports

3.2.1 CARM data

Duro-Tuss and Difflam are brand names for various combination cough mixtures, some of which contain pholcodine. Reports submitted to CARM may not always state whether the product contains pholcodine (for example, reports may just state 'Duro-Tuss'). Due to the lack of certainty about the specific product that was reported, only reports in which pholcodine was specifically listed are reviewed here.

Reports to CARM with cut-off date 30 September 2019:

21 spontaneous reports to CARM where pholcodine was specifically stated in the report as a suspect medicine (Table 19) not highlighted in grey). The majority of these reports were for allergic-type reactions, including two reports of anaphylaxis.

Reports to CARM from 1 October 2019 to 31 March 2023:

There were an additional 6 cases reported to CARM during this period (Table 19, highlighted in grey). Similar to the previous period, the majority of the reports were for allergic-type reactions.

Table 20: CARM case reports for pholcodine (suspect medicine in bold) as of 31 March 2023

Report ID	Date	Age/Sex	Medicine(s)	[redacted]	Reactions(s)
002876	Aug 1971	7m M	**Pholcodine** **Codeine** Acetylsalycylic acid Erythromycin estolate		Hypoventilation Apnoea Hypotonia Miosis Restless
004285	Oct 1973	0 F	**Phenylzine** **Pholcodine** **Phenylephrine** **Chlorpheniramine**		Headache Vomiting Abdominal pain Therapeutic response increased
006822	Oct 1977	69 F	**Pholcodine** Aminophylline **Methdilazine** Guaiphenesin		Face oedema Bronchospasm Rash
013928	Aug 1985	55 F	Cotrimoxizole **Pholcodine**		Rash maculo-papular
018198	Dec 1988	28 F	**Pholcodine** Triphasil		Urticaria Oedema
024434	Jun 1993	38 F	**Erythromycin ethylsuccinate** **Pholcodine**		Rash erythematous Oedema periorbital
033581	Feb 1997	67 F	**Pholcodine**		Vomiting Diarrhoea

[redacted]

				[redacted]	Sweating increased Abdominal pain
033753	Feb 1997	28 M	**Pholcodine**		Vomiting
035772	Sep 1997	8m M	**Pholcodine**		Rash Oedema
039569	Oct 1998	40 F	**Pholcodine**		Vomiting Pruritis Flushing Bronchospasm
042742	Aug 1999	17 F	**Pholcodine** Paracetamol		Face oedema Pruritis Flushing
043027	Nov 1999	37 F	**Pholcodine** **Ciprofloxacin** Triphasil		Taste loss Anosmia Vision abnormal
048326	Aug 2001	72 M	**Pholcodine**		Rash
051449	May 2002	24 F	**Pholcodine** Paracetamol		Palpitation Sleep disturbed
059934	Apr 2004	60 F	**Pholcodine**		Rash Pruritus
061462	Jul 2004	33 F	**Pholcodine**		Vision abnormal
068413	Sep 2005	- M	**Pholcodine**		Pruritus

084894	Jun 2009	43 M	**Pholcodine** **Amoxicillin/clavulanic acid** Menthol Eucalyptus	[redacted]	Angioedema Conjunctivitis Dizziness
086809	Oct 2009	21 M	**Pholcodine** **Codeine** **Morphine sulphate**		Allergy
114715	Dec 2014	63 F	**Pholcodine**		Anaphylactic reaction
118693	Nov 2015	69 F	**Pholcodine**		Anaphylactic reaction
134615	Oct 2019	24 F	**Pholcodine** **Rocuronium** Glycopyronium bromide Fentanyl Propofol		Urticaria Skin test negative Bronchospasm Blood immunoglobulin E abnormal
135551	Dec 2019	82 M	**Pholcodine** Amlodipine Fluticasone		Anaphylactic reaction Blood immunoglobulin E abnormal
141397	June 2021	33 F	**Pholcodine** Potassium iodate		Urticaria Dizziness
142377	Oct 2021	74 M	**Pholcodine**		Anaphylactic reaction Medication error

144610	Aug 2022	30 F	**Pholcodine** Escitalopram Methylphenidate Fluticasone Evening primrose oil	[redacted]	Anaphylactic reaction Drug specific antibody
146046	Dec 2022	69 M	**Pholcodine** **Amoxicillin/clavulanic acid** **Doxycycline** Atorvastatin Enalapril		Angioedema

Notes:

Case reports highlighted in grey received between the period 1 October 2019 to 31 March 2023.

UNK = unknown.

Comments:

Due to the nature of spontaneous reporting, it is difficult to establish whether there have been local cases of NBMA-pholcodine cross-sensitisation. Not all cases of anaphylaxis are reported to CARM. Case details and test results may not always be provided in the case narrative.

CARM 114715 describes anaphylaxis following pholcodine consumption [redacted]

CARM 134615 describes a case of allergic reaction [redacted] with various anaesthesia, including rocuronium [redacted]

CARM 135551 and 144610 describes cases of anaphylaxis following pholcodine consumption. [redacted]

Case reports of anaphylaxis following NMBAs were reviewed for the period 2019 to 2022. [redacted]

3.2.2 Word Health Organization Global Database

VigiBase is the World Health Organization's global database containing Individual Case Safety Reports (ICSRs) submitted by over 130 countries. Some participating members may submit ICSRs even when the medicine was not considered the suspect medicine.

[redacted]

3.3.1 European Medicines Agency [1, 45]

On 1 December 2022, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) concluded its review on pholcodine and recommended the market authorisation for products containing pholcodine be revoked.

The PRAC recommendations were sent to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). This recommendation was endorsed by the CMDh and finalised by the European Commission on 6 March 2023.

A summary of PRAC's review is outlined below. Refer to Annex 2 for the EMA assessment report, which includes a summary of the literature and post-marketing data considered.

Data on the risk of anaphylaxis:

Literature:

The PRAC made the following comments on the ALPHO study:

- The main uncertainty is the detection of other factors associated with the risk of a perioperative anaphylactic with NMBAs, such as occupational exposure to quaternary ammoniums. Significantly more patients with occupational exposure to quaternary ammoniums were included into case versus control populations (approximately 5.4 vs. 19.8%, $p < 0.0001$).
- Limitations regarding establishing prior pholcodine consumption was noted.
- Despite these limitations, the study was adequately designed and adds to the cumulative evidence from literature reports and previous epidemiological studies that pholcodine is an important risk factor for NMBA-related anaphylaxis. Based on the totality of evidence a causal relationship between pholcodine use and NMBA-related anaphylaxis is considered sufficiently established.

For the Australian study by Sadleir et al (2021), the following comments were noted:

- There are differences in anaesthesia practices in Australia versus Europe and therefore the results from the Australian study could not be fully extrapolated to the EU. There were several limitations in this study, such as representativeness of patient population, recall bias to pholcodine exposure, possible misclassification of cases, different use of NMBAs compared to the EU and power of the study.

Post-marketing data:

Cumulatively from the MAH safety databases or in EudraVigilance, there were 24 cases containing a MedDRA Preferred Term from the SMQ Anaphylactic reaction where pholcodine-containing medicine was the suspected or interacting medicine with relation to NMBA. Of these, 14 cases were serious. Three cases reported a fatal outcome. Where reported, pholcodine exposure and onset of anaphylaxis ranged between 2 and 3 months.

Most cases originated from France or Australia, and it is possible that these cases have already been published in studies mentioned earlier in the report.

Risk Minimisation Measures proposed by Sponsors:

Risk minimisation measures were proposed by the Sponsor. Each measure was discussed by the PRAC but overall were not considered effective at reducing the risk of perioperative anaphylaxis for an individual patient exposed to pholcodine.

- Updating the pholcodine product information to instruct clinicians to inquire a patient's exposure to pholcodine in the last 12 months prior to a procedure. In the case of confirmed previous use of pholcodine, sIgE to QAI/pholcodine and/or skin tests should be used prior to the procedure – the PRAC considered this was not an effective measure as patients or healthcare professionals could be unaware of the use, especially in the last 12 months.
- Contraindicating pholcodine use in patients with a previous allergic reaction to NMBAs – the PRAC considered this would not minimise the risk. Patients can develop an allergic reaction to NMBA even if not previously exposed to an NMBA.
- Up-scheduling pholcodine to a prescription-only medicine – the PRAC considered that this measure would only limit the use of pholcodine but not the risk.
- Restricting the therapeutic indication of pholcodine for example, as a second line treatment – the PRAC considered that this would reduce usage, but not reduce the risk of perioperative anaphylaxis to NMBAs. Some therapeutic alternatives in the EU were codeine, ethylmorphine, dextromethorphan and butamirate.
- Creating a patient 'alert card' to ensure that special information regarding a patient is communicated prior to any operative procedure. The patient alert card is to be held by patient at all times in order to

reach the relevant healthcare professional when needed – the PRAC considered that this tool would not be an effective since pholcodine is only used briefly. Patient should not be expected to hold a card months after pholcodine treatment has stopped
- Issuing a Dear Healthcare Professional Letter informing healthcare professionals of the risk and the need to take certain actions and cautiously adapt their practices in relation to a previous pholcodine exposure – the PRAC considered that even if anaesthetists are well informed about the risk, it will not help them in their practice as they cannot predict which patients will develop cross-sensitisation and reactions to NMBAs.
- Updating the NMBA product information.

The PRAC could also not identify measures that would allow healthcare professionals to identify which patients treated with pholcodine will develop cross-sensitisation and anaphylactic reactions to NMBAs.

The decision to use a NMBA during anaesthesia is based on clinical necessity and cannot be avoided in any subpopulation, regardless of history of pholcodine use.

Data on the efficacy of pholcodine:

The totality of available data suggests that the efficacy of pholcodine-containing medicines for the symptomatic treatment of non-productive cough is established considering the marketing authorisations for these medicinal products as well as the conclusions on efficacy in the previous CHMP referral in 2011. No new efficacy data became available since the 2011 referral.

Benefit-risk balance:

The totality of available data suggests that the efficacy of pholcodine-containing medicinal products in symptomatic treatment of non-productive cough is considered established.

Perioperative anaphylaxis to NMBA is rare (1/10.000 anaesthesia procedures) but a serious and threatening event, with a relatively high mortality (4-6%).

No specific characteristics for perioperative anaphylactic reaction to NMBA could be identified in patients who have been treated with pholcodine, and therefore all these patients are considered at risk. Therefore, all available measures should be taken to decrease its incidence.

NMBA during anaesthesia is based on clinical necessity and cannot be avoided in any subpopulation, regardless of the history of pholcodine use. The PRAC could also not identify measures that would allow healthcare professionals to identify which patients treated with pholcodine will develop cross-sensitisation and reactions to NMBAs. In addition, the PRAC could not identify conditions which if fulfilled would demonstrate a positive benefit-risk balance for pholcodine-containing medicinal products in a defined patient population.

In the EU there are alternatives for the treatment of dry cough.

The PRAC concluded that the risk of perioperative anaphylactic reaction related to NMBAs outweighs the benefits of pholcodine in the treatment of non-productive cough, a symptomatic indication considered acute and not serious.

A communication was published including information about the medicine and procedure and information to patients and healthcare professionals [45].

3.3.2 Therapeutic Goods Administration [46]

Pholcodine was a pharmacy-only medicine in Australia.

The Therapeutic Goods Administration (TGA) investigated the safety issue following the EMA's recommendation to withdraw pholcodine-containing products. The TGA considered that the recommendations made by the EMA and the results of the ALPHO study are applicable to the Australian population. This is supported by the study by the Western Australian study by Sadleir et al (2021).

The TGA's Database of Adverse Event Notifications (DAEN)- external site on 9 February 2023 identified 50 Australian case reports of NMBA anaphylaxis with either previous pholcodine use or test results indicating increased hypersensitivity to pholcodine. Sixteen of these cases have been published in the literature. There was 1 fatality.

Similar to the PRAC's recommendation, the TGA considered that:

- Patients who require local anaesthetics are typically asked about prescription medicines, however hospitals and surgery facilities do not consistently ask about OTC medicines, especially if such use was some months earlier.
- There are safer alternatives to treat dry coughs.
- Given it is difficult to reliably predict who may be at risk of anaphylaxis to NMBAs and the seriousness of the safety risk for pholcodine-containing medicines, a recall of pholcodine-containing medicines was made, and the cancellation of these medicines' registrations took effect on 29 March 2023.

The TGA have published several communications:

- Pholcodine – 28 February 2023.
- Pholcodine cough medicines cancelled by the TGA and recalled from pharmacies for safety reasons – 28 February 2023.
- Check for pholcodine use before general anaesthesia – 17 March 2023.

3.3.3 United Kingdom's Medicines and Healthcare products Regulatory Agency

Pholcodine-containing medicines were Pharmacy (P) only medicines and therefore had only been sold or dispensed under the supervision of a suitably trained healthcare professional [47].

The Commission on Human Medicines (CHM) considered that there was sufficient overall evidence for an association of NMBA anaphylaxis with pholcodine, although the absolute risk of anaphylaxis remains very small. There was a lack of identifiable effective measures to minimise the increased risk of anaphylactic reactions to NMBAs [48].

On 14 March 2023, the MHRA published a communication advising that pholcodine-containing medicines will be withdrawn from the UK market as a precautionary measure [48]. The communication included a summary of the pholcodine review by MHRA, advice for healthcare professionals and advice for healthcare professionals to provide to patients. A class 2 medicines recall was also issued requiring pharmacists to quarantine all remaining stock and return to the supplier [47].

3.4 Company review under section 35 of the Medicines Act 1981

On 5 April 2023, the Sponsors of pholcodine-containing medicines were notified that their products were being considered under section 35 of the Medicines Act 1981 (the Act).

The Act provides:

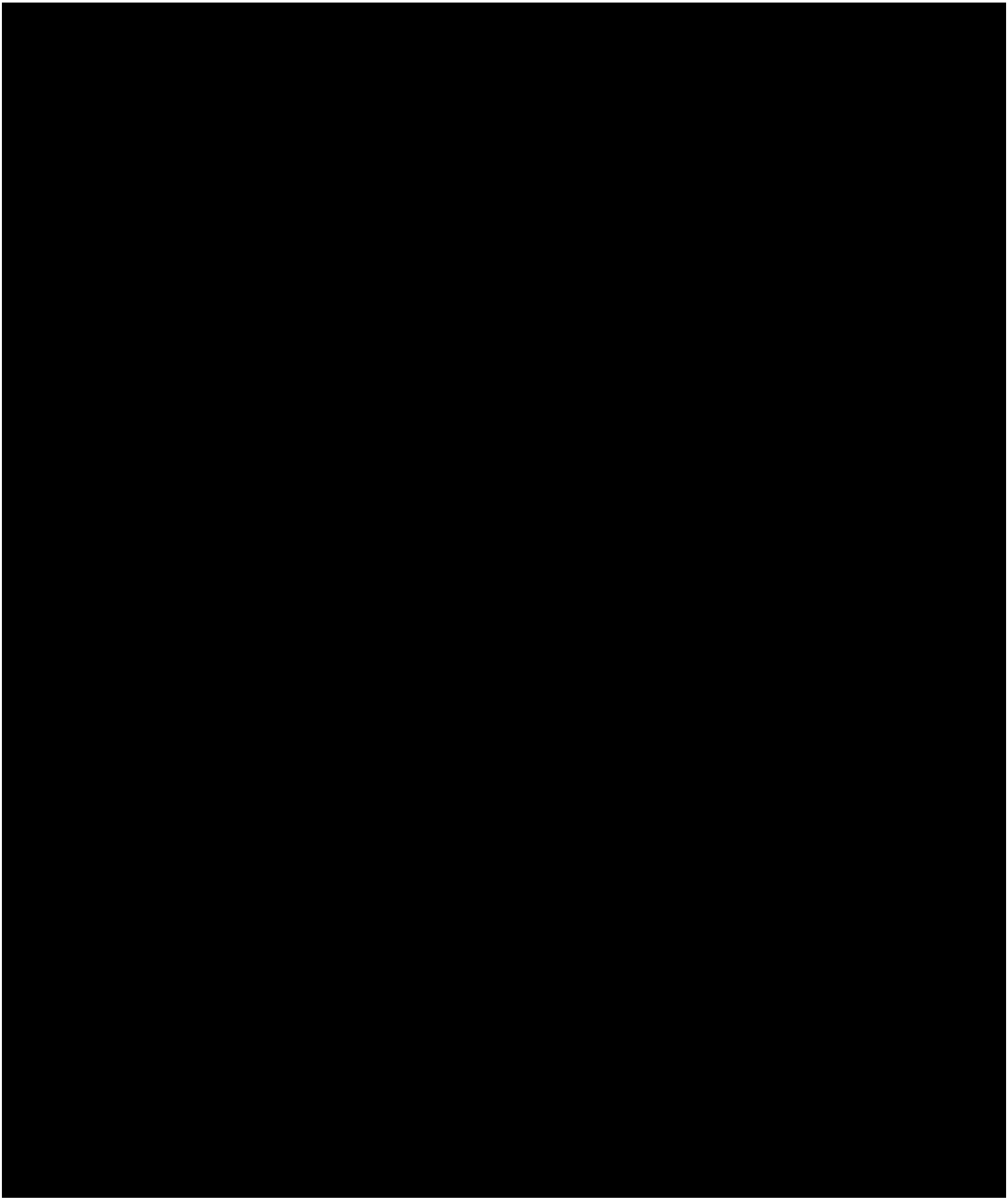
> **35 Revocation and suspension of consents**
>
> (1) The Minister may at any time, by notice, revoke, or suspend for such period as he may determine, any consent given under section 20 or section 23, if he is of the opinion that—
>
> (a) the medicine can no longer be regarded as a medicine that can be administered or used safely for the purposes indicated in the application for consent, or in a notice deposited under section 24; or
>
> (b) the specifications and standards with respect to the manufacture of the medicine that were included in the terms of a consent can no longer be regarded as satisfactory; or
>
> (c) the efficacy of the medicine can no longer be regarded as satisfactory.

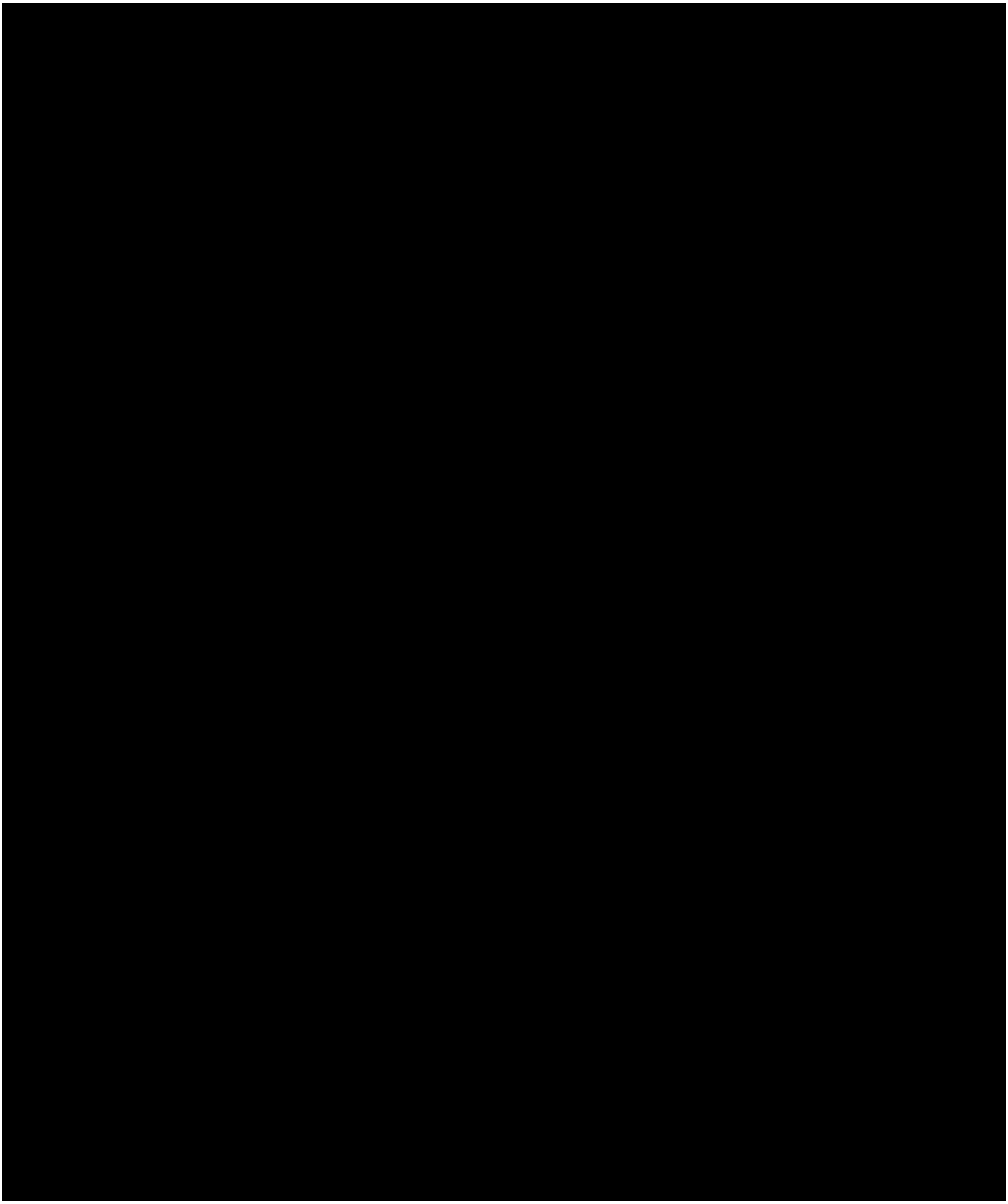
To consider whether regulatory action is required under the Act, the Sponsor was informed that Medsafe

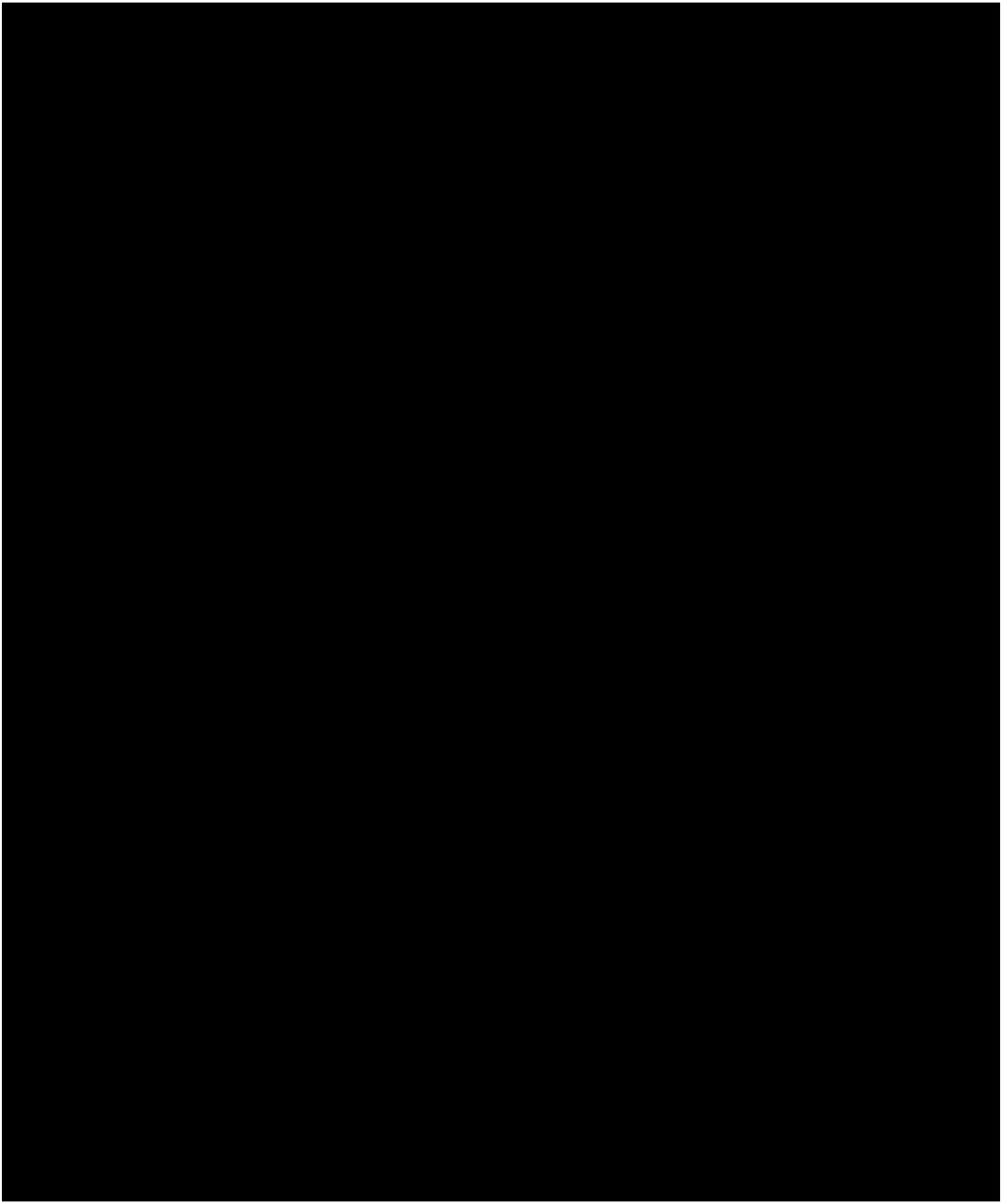
would review the safety and efficacy of pholcodine-containing products. The Sponsors were also given the opportunity to submit the following supporting information for Medsafe to consider in the review.

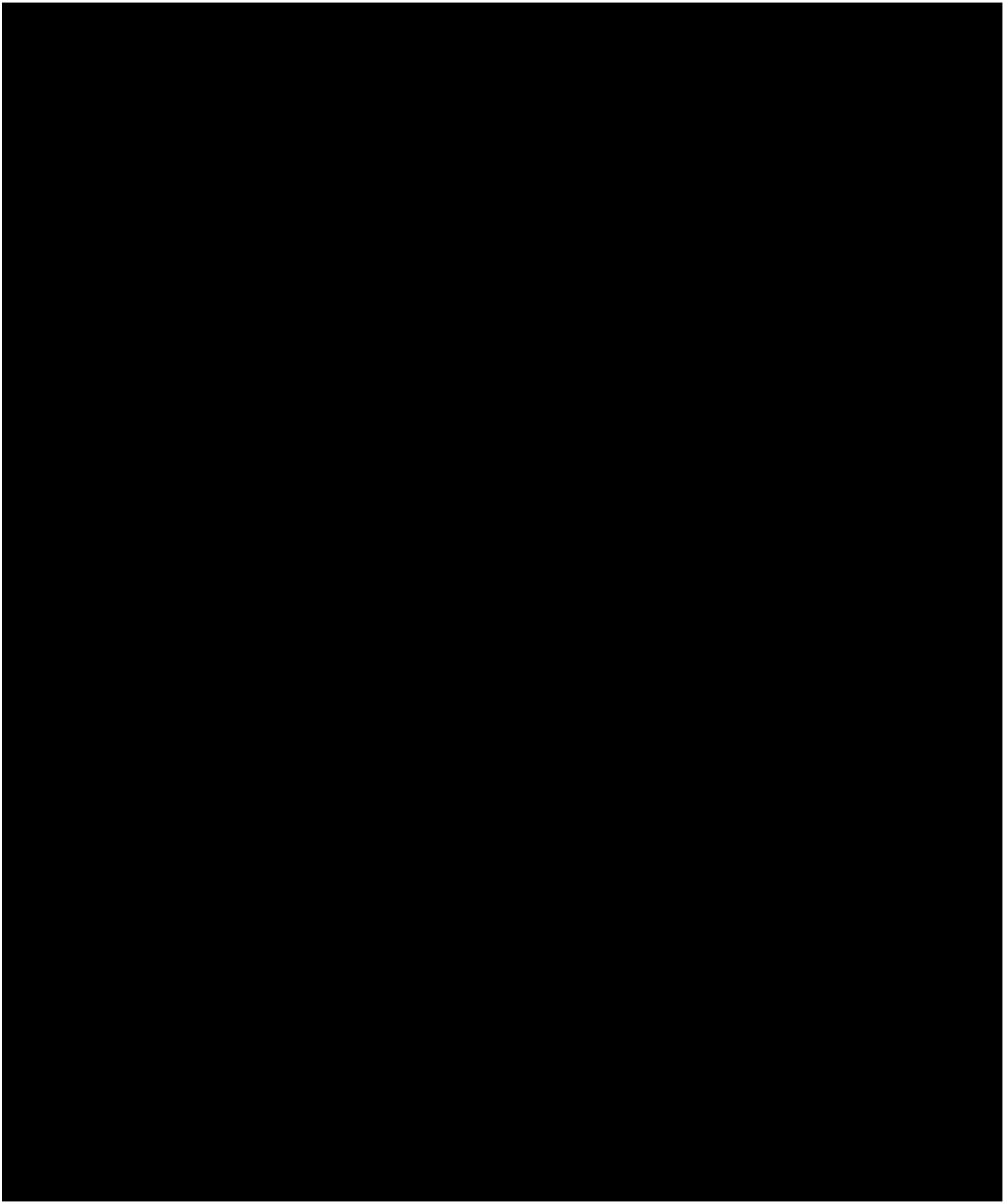
1. The Sponsor's position on the efficacy and safety of pholcodine, in light of the recent withdrawal of pholcodine in other countries.
2. Evidence of efficacy and safety – to support that pholcodine can still be regarded as a medicine that can be administered or used safely for the purposes indicated in the application for consent; and that the efficacy of the medicine can still be regarded as satisfactory.
3. To provide proposals for risk minimisation plans for New Zealand, if the Sponsors believe their product(s) should remain on the market.
4. Any other relevant information.

[redacted]









[redacted]

3.5 Submission from third parties

On 26 April 2023, Medsafe published a monitoring communication. The aim of this communication was to inform the public that Medsafe was reviewing whether pholcodine-containing products should continue to be available and to seek feedback from consumers and healthcare professionals on the use of pholcodine for the symptomatic relief of dry coughs.

Medsafe received 11 submissions (from individuals and an organisation). The submissions are copied verbatim below (with individual names/identifying information removed).

[redacted]

These continue to have a small but important place in managing cough. I would not want to see them go.

[redacted]

I believe pholcodine based cough medicines should continue to be available via prescription only. But it should not be withdrawn completely.

Advising to use this is often one of the only reasons patients are happy not to be prescribed antibiotics. And by careful prescriptions we can minimize adverse reactions such as anaphylaxis.

It would be in my opinion that we should continue to have this as an option.

[redacted]

In my view the restriction applied in Dec 2022 is sensible ensuring the products are available to patients that need them from pharmacists.

[redacted]

Pholcodine is a useful medicine providing symptomatic relief to many people. Alternatives such as codeine are more problematic. The risk of a rare side effect occurring in some very unlikely situations would not seem to justify a ban on all use.

[redacted]

Increasingly coughs and colds, particularly irritating dry coughs are challenging to deal with for symptomatic care.

We have had restrictions on Gees linctus and nationwide shortages.

For a proportion of people, pholcodine in many dry cough products is soothing and enables them to sleep - which is the major reason why they visit the doctor so they can keep working during the day.

In the absence of anything better and in the desire not to further overburden primary care with more people with dry irritating coughs that we can't (and shouldn't) prescribe antibiotics for. I would endorse having these products still available. If they need to be restricted to a quick chat with the pharmacist this seems reasonable - however I request that they not be banned altogether.

[redacted]

I found the Pholcodine linctus 5mg and 10mg very useful for patients. Especially those with a post viral cough that can go on for several weeks.

More effective when used with hot water

I don't think the weaker strength and lozenges were useful.

[redacted]

The purpose of this email is to raise concern that the withdrawal of pholcodine leaves very few options to the treatment of a dry cough and will reduce access to options for treatment in the community putting pressure on general practice with simple requests for care. Should there be a withdrawal of this product then there should be suitable alternative that a pharmacist may prescribe.

[redacted]

It is important to note that not all surgeries require general anaesthesia and neuromuscular blocking agents. Some surgeries may only require local anaesthesia, which does not carry the same risk for anaphylaxis.

However, patients who receive general anaesthesia involving neuromuscular blocking agents (NMBAs) during surgery are at an increased risk of anaphylaxis if they have been exposed to pholcodine in the past. While pholcodine may not be needed for certain surgeries, it is still used for the treatment of cough in other patients.

However, due to the risk of anaphylaxis in patients who receive general anaesthesia involving NMBA during surgery, I understand, it is important to weigh the benefits and risks of using pholcodine in these patients.

In light of the information provided, I would like to offer my feedback that reclassifying pholcodine-containing medicines as prescription-only medications might be a more appropriate course of action rather than withdrawing them from the market completely. This would allow for the inclusion of an interaction warning on the New Zealand Formulary, which could alert healthcare professionals to the potential risk of anaphylaxis during general anaesthesia involving NMBAs. By requiring a prescription for pholcodine, prescribers and pharmacists can ensure that patients are aware of this risk and take appropriate precautions.

I would like to provide my perspective on the potential impact of withdrawing pholcodine from the market. While patient safety should always be the top priority, it is important to consider the potential economic impact as well. There is a scarcity of cough syrups in the market. This could have a ripple effect on various industries, including the pharmaceutical industry, as well as businesses. Considering the significance of supply and demand in trading, and any disruption to the availability of cough suppressants could have a negative effect on the industry and the economy as a whole. Given the current inflation in New Zealand, it is important to carefully consider the impact of any decision to withdraw a medication or any stock from the market. With that in mind, instead of taking pholcodine-containing medicines completely out of the market, it may be more appropriate to consider reclassifying them as prescription-only medications.

[redacted]

There seems to be a lack of good evidence for efficacy, plus anaphylaxis risk, so I think withdrawing pholcodine from the market is feasible. [redacted] the sale has become more risk mitigation and gatekeeping rather than a positive recommendation for use.

[redacted]

I have talked to several customers over the past month. Responses have been

1- want to use something else

2- one person had been sold it at another pharmacy and had not been given any of the warning information. He had recently had several operations and there was a possibility on further within the coming year.

Younger people 20-35 yr are more likely to say they will buy it as surgery unlikely.

The older ages are more cautious.

My thoughts are given the length of time it can have the risk then it would be safer to remove it or move to prescription only where pharmacists can prescribe only if they have completed the necessary training to ensure appropriate counselling is given.

[redacted]

Considering the recent evidence, the recall of pholcodine by regulatory authorities in other countries, and lack of suggested effective measures to minimise the risk, we recognise the benefit of pholcodine in the symptomatic treatment of a non-productive (dry) cough is moderate to low, and the risk of an anaphylactic reaction to be far greater and could be potentially life-threatening, unpredictable, and persistent for several months after exposure.

Taking into account that pholcodine is only used to treat the non-life threatening self-limiting functional symptoms of a non-productive cough with spontaneous resolution, we support the full withdrawal of all pholcodine-containing products from the New Zealand market, with the clear understanding that this would be a full Class 1 product recall at pharmacy/retail level, and that pharmacies will be able to return all unused stock (even broken original packs) for full reimbursement.

Should the Class 1 product recall be at consumer level, we request that an administration fee be paid to pharmacies per unit returned to compensate for any administration time staff would have to dedicate to this, adding to workforce pressures.

Comments:

11 submissions were received, possibly due to the short time available for submissions so it is difficult to know if the responses truly reflect healthcare professionals' views on pholcodine. Feedback from consumers were not received.

Most [redacted] expressed that they wanted pholcodine to continue being available. Issues raised included the lack of alternative dry cough options, added pressures to primary care, and losing an option to satisfy patients not being able to have antibiotics.

There were mixed views in regards to the efficacy of pholcodine. Some respondents gave anecdotal accounts that pholcodine was effective.

Three respondents suggested up-scheduling pholcodine to a prescription-only medicine while 2 respondents considered the current classification appropriate to manage the safety risk.

3.6 Risk minimisation measures and options

This section discusses potential risk minimisation measures and their feasibility in the New Zealand context.

Medicine classification

The current restricted classification of pholcodine requires a consultation with a pharmacist prior to sale. Although this will limit the use, it does not reduce the risk of NMBA-related anaphylaxis. At the current time, no risk factors for NMBA-related anaphylaxis can be identified in patients exposed to pholcodine, therefore everyone exposed to pholcodine is at risk should they require a NMBA during surgery. Healthcare professionals will not be able to identify a patient population that would benefit from pholcodine treatment and not be at risk.

Healthcare professionals can advise consumers about the risk of NMBA-related anaphylaxis. However, consumers may not appreciate this important information at the time particularly if they do not anticipate undergoing surgery. In addition, it is not possible to predict who will need anaesthesia in the future. The same concept applies if pholcodine is up-scheduled to a prescription medicine.

Communication and educational activities

These include publishing safety communications, writing letters to relevant professional bodies, and requesting Sponsors to produce a Dear Healthcare Professional Letter.

Anaesthetists are the main healthcare professionals involved in using NMBAs and are already well informed about this risk of sensitisation with pholcodine. ANZCA have repeatedly highlighted this safety concern to their members.

It is unlikely that additional communication or educational activities would be effective at minimising NMBA-related anaphylaxis related to prior pholcodine consumption. Managing perioperative anaphylaxis is challenging and clinicians cannot predict which patients will develop cross-sensitisation and reactions to NMBAs. In addition, the decision to use a NMBA during anaesthesia will be based on clinical necessity which may not be avoided in any subgroups, regardless of history of pholcodine use.

Prior to surgery, clinicians could routinely ask patients whether they have been exposed to pholcodine in the last 12 months. However, as highlighted in the ALPHO study, it is difficult to establish this as patients may not always remember what medicines they are taking, particularly if purchased OTC and used only briefly. In addition, there is no quick and reliable way to ascertain previous pholcodine use when NMBA is required in acute unplanned procedures or when the patient is unconscious.

It is also not clear whether 12 months is the correct time period after which there is no risk as data beyond this time period was not available in the ALPHO study. Data from an earlier study in Norway suggests that the risk may persist for up to 3 years based on IgE levels [48, 49].

Updates to the pholcodine data sheet and package labelling

The pholcodine data sheets have information on pholcodine sensitisation to NMBAs in section 4.4. This section could be strengthened with the results of the ALPHO study.

No patient specific risk factors associated with pholcodine-induced NMBA sensitisation has been identified to enable the introduction of a contraindication to the data sheet.

Screening prior surgery

The results of the ALPHO study showed a low positive predictive value of sIgEs, meaning a result of a positive test cannot be used to accurately determine if a patient will be at risk of NMBA-related anaphylaxis. The high negative predictive value means a negative test result can indicate a low risk of NMBA-related anaphylaxis.

Considering the rarity of perioperative anaphylaxis and potentially large number of patients exposed to pholcodine, testing would require a cost-benefit analysis.

Testing may not be practical in many clinical settings such as emergency situations where administration of NMBAs is urgently needed. In New Zealand, there may be issues having easily accessible laboratory and skin tests.

Choice of NMBA use

This measure does not specifically lower the risk of NMBA-related anaphylaxis from pholcodine exposure. However, the choice of NMBA used may potentially lower the overall risk of anaphylaxis as there appears to be differences in the rate of anaphylaxis among NMBAs.

In the Western Australian study by Sadleir et al (2021), the rate of anaphylaxis for rocuronium was 3 times that of vecuronium. The Auckland study by Reddy et al (2015) found the rate of anaphylaxis was higher in patients receiving rocuronium and suxamethonium compared to other NMBAs. The results of the ALPHO study showed that any NMBA was implicated in anaphylaxis.

Clinicians could consider avoiding certain NMBAs, however this needs to be weighed against the availability of the NMBA. In addition, it may not be possible to avoid certain NMBAs as the choice will depend on patient factors, co-morbidities, type of procedures being performed, and the clinical indication.

4 DISCUSSION AND CONCLUSIONS

Overview

In 2019, the MARC considered that the risk-benefit balance of pholcodine for the symptomatic relief of dry cough was marginal. At the time there was insufficient evidence to indicate an unfavourable risk-benefit balance. There was no clear causal association between prior pholcodine exposure and the risk of NMBA-related anaphylaxis, although an ecological association was noted. More recently, retrospective studies by Mertes et al (2023) and Sadleir et al (2021) add to the cumulative evidence from literature reports and previous studies linking pholcodine with NMBA-related anaphylaxis.

In 2022, the EMA concluded that the risk of life-threatening perioperative anaphylaxis related to NMBAs outweighs the benefit of pholcodine in the treatment of non-productive cough, a symptomatic indication considered acute and not serious. Subsequently, pholcodine has been withdrawn from the EU market. Where pholcodine is available, other regulators such as the United Kingdom, Australia and Malaysia have followed suit.

The MARC is asked to consider the efficacy and safety of pholcodine and provide recommendations to the Minister's delegate in their considerations under s35 of The Act.

Consideration of the efficacy of pholcodine

No new efficacy data became available since the 2019 risk benefit review. The available clinical efficacy data is limited, which includes 9 clinical studies of which 8 were published prior to 1990. Most of the studies were

small, had poor patient selection, were not adequately controlled with either active or placebo. In some studies, pholcodine was used in combination products so that it was not possible to attribute any observed effect solely to pholcodine. The lack of demonstrated efficacy for pholcodine is a factor of the age of the medicine and does not necessarily imply inefficacy.

There is absence of good quality studies comparing pholcodine versus other treatments for cough (eg, codeine, dextromethorphan, honey and glycerol). This makes comparison to alternative products difficult.

A 2006 study compared pholcodine and dextromethorphan in patients with acute cough. Both medicines had similar effect on cough, but pholcodine had fewer treatment-emergent adverse events. The study did not have a placebo arm so any observed improvement in cough is difficult to distinguish from natural recovery versus treatment.

Honey is another alternative treatment. A meta-analysis showed that honey was superior to usual care in reducing cough frequency and severity. In this analysis, usual care included dextromethorphan. A Cochrane review showed that honey can relieve cough symptoms in children to a greater extent than no treatment, diphenhydramine and placebo.

Lastly, glycerol may contribute to the efficacy of cough syrups due to its demulcent and humectant properties. There are however no studies comparing the cough suppressant effect against placebo.

Consideration of the safety of pholcodine

There is limited safety data for pholcodine. There are no adequate clinical trials for either short-term or long-term safety.

Case reports in the literature describe mainly dermatological reactions. There have also been cases of fatal pholcodine intoxication.

As of 31 March 2023, most case reports to CARM report a hypersensitivity spectrum reaction to pholcodine, including cases of anaphylaxis. [redacted]

The main safety concern identified for pholcodine is a risk of perioperative anaphylaxis to NMBA from pholcodine cross-sensitisation. Perioperative anaphylaxis is a relatively rare event, but is nonetheless a life-threatening event that may cause significant morbidity and mortality. The mortality rate ranges from 4 to 6% despite accessible management. NMBAs account for approximately 60% of perioperative anaphylaxis in Europe and Australia.

The ALPHO study concluded that both occupational exposure to QAIs and pholcodine can induce cross-sensitisation to NMBA and subsequent anaphylaxis. Although there are some limitations to this study as noted above. It is not possible to eliminate or control the vast amount of QAIs found in the environment, however pholcodine represents a substance which exposure can be controlled or eliminated to minimise cross-sensitisation. It should also be noted that removal of pholcodine will not eliminate the risk of anaphylaxis to NMBA cross reactivity completely.

In patients with prior pholcodine exposure and requiring NMBAs, no effective minimisation measures have been identified given there are no known risk factors for NMBA-related anaphylaxis, the difficulty in ascertaining prior pholcodine consumption in patients requiring planned or unplanned surgeries, and that no tests can accurately identify patients at risk particularly in acute settings.

5 ADVICE SOUGHT

The Committee is asked to advise whether:

- The evidence of an association between pholcodine use and an increased risk of anaphylaxis from NMBAs is now sufficient to require regulatory action?
- In line with the section 35 of the Medicines Act 1981 (the Act) procedure, if pholcodine:
    - no longer can be regarded as a medicine that can be administered or used safely for the symptomatic relief of dry (non-productive) cough OR

    - the efficacy of pholcodine no longer can be regarded as satisfactory.
- OR whether regulatory action not related to the Act best fits the information reviewed in this paper (for example changes to the data sheet)?

6 ANNEXES

Annex 1 – Pholcodine risk benefit review December 2019 MARC report (unredacted).

Annex 2 – EMA Pholcodine-containing medicinal products Assessment Report: Procedure number: EMEA/H/A-107i/1521.

[redacted]

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