s22

From: s22 @sanofi.com>
Sent: Tuesday, 13 December 2022 5:09 PM
To: PEGG, Grant; Signal Investigation Coordinator
Cc: chc.ae; s22 /AU; s22 /AU; s22
Subject: RE: Significant Safety Issue- Pholcodine [SEC=OFFICIAL]
Attachments: ALPHO_Rapport Final_15092022.pdf

Dear Grant,

Please find attached ALPHO Study results as requested by the TGA.

We will provide an update related to our Pholcodine product before end of this week. We would appreciate an opportunity to speak with you to understand and align on next steps. Would it be possible to have a meeting next week to discuss this.

Thank you.

Kind Regards

s22
s22
Consumer Healthcare
Mb. s22
s22 @sanofi.com
Building D, 12-24 Talavera Road
Macquarie Park, NSW 2113

sanofi

From: PEGG, Grant
Sent: Tuesday, 13 December 2022 11:47 AM
To: s22 /AU ; Signal Investigation Coordinator
Cc: chc.ae ; s22 /AU ; s22 /AU ; s22
Subject: RE: Significant Safety Issue- Pholcodine [SEC=OFFICIAL]

Hi s22,

Can you please provide an update as to when this information will be available?

I'm happy to discuss this on telephone if required.

Thanks,

Grant

Dr Grant Pegg
Principal Medical Advisor– Pharmacovigilance Branch s22 [redacted]
s22 [redacted]

Medicines Regulation Division | Health Products Regulation Group
Australian Government Department of Health and Aged Care
E s22 [redacted] @health.gov.au
Location: TGA Building, Scherger Lane, Fairbairn, ACT, 2609
PO Box 100, Woden ACT 2606, Australia

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s22 [redacted] /AU s22 [redacted] @sanofi.com>
Sent: Wednesday, 7 December 2022 1:08 PM
To: Signal Investigation Coordinator <si.coordinator@health.gov.au>
Cc: chc.ae <chc.ae@sanofi.onmicrosoft.com>; s22 [redacted] /AU s22 [redacted] @sanofi.com>; s22 [redacted] /AU s22 [redacted] @sanofi.com>; s22 [redacted] s22 [redacted] @health.gov.au>
Subject: RE: Significant Safety Issue- Pholcodine [SEC=OFFICIAL]

REMINDER: Think before you click! This email originated from outside our organisation. Only click links or open attachments if you recognise the sender and know the content is safe.

Dear s22 [redacted],
We acknowledge the receipt of this email. We will provide the requested information as soon as possible.
Thank you.
Kind Regards

s22 [redacted]
s22 [redacted]
Consumer Healthcare
Mb. s22 [redacted]
s22 [redacted] @sanofi.com
Building D, 12-24 Talavera Road
Macquarie Park, NSW 2113

From: Signal Investigation Coordinator
Sent: Wednesday, 7 December 2022 12:41 PM
To: s22 [redacted] /AU
Cc: chc.ae ; s22 [redacted] /AU ; s22 [redacted] /AU ; s22 [redacted]
Subject: RE: Significant Safety Issue- Pholcodine [SEC=OFFICIAL]
Dear s22 [redacted]
The TGA requests that Sanofi please provide the final results of the ALPHO study and advise of any plans for regulatory action in Australia with regards to BISOLVON PHOLCODINE DRY FORTE.
Thank you and kind regards
s22 [redacted]

s22 [redacted]
Medicines Surveillance and Targeted Review, Medicines and Vaccines Investigation and Surveillance
Pharmacovigilance Branch

s22 [redacted]

Therapeutic Goods Administration
Australian Government, Department of Health and Aged Care
PO Box 100
Woden ACT 2606
www.tga.gov.au

From: s22 [redacted] /AU s22 [redacted] @sanofi.com>
Sent: Tuesday, 6 December 2022 12:20 PM
To: Signal Investigation Coordinator <si.coordinator@health.gov.au>
Cc: chc.ae <chc.ae@sanofi.onmicrosoft.com>; s22 [redacted] /AU s22 [redacted] @sanofi.com>; s22 [redacted] /AU s22 [redacted] @sanofi.com>
Subject: RE: Significant Safety Issue- Pholcodine

Dear s22 [redacted]

Sanofi Healthcare Pty. Ltd. wants to notify the TGA of EMA's decision for pholcodine containing medicines in the EU.

EMA's safety committee, PRAC, has concluded its review of medicines containing pholcodine, which are used in adults and children to treat non-productive (dry) cough and, in combination with other active substances, for the treatment of symptoms of cold and flu, and has recommended the revocation of the EU marketing authorisation for these medicines.

During the review, the PRAC evaluated all available evidence including the final results of the ALPHO study, post-marketing safety data and information submitted by third parties such as healthcare professionals. The available data showed that use of pholcodine in the 12 months before general anaesthesia with neuromuscular blocking agents (NMBA) is a risk factor for developing an anaphylactic reaction (a sudden, severe and life-threatening allergic reaction) to NMBAs.

As it was not possible to identify effective measures to minimise this risk, nor to identify a patient population for whom the benefits of pholcodine outweigh its risks, pholcodine-containing medicines are being withdrawn from the EU market and will therefore no longer be available by prescription or over the counter.

Should we become aware of any additional information related to this SSI, we will inform the TGA as soon as possible.

Thank you.

Kind Regards

s22 [redacted]
s22 [redacted]
Consumer Healthcare
Mb. s22 [redacted]
s22 [redacted] @sanofi.com
Building D, 12-24 Talavera Road
Macquarie Park, NSW 2113

From: Signal Investigation Coordinator
Sent: Tuesday, 8 November 2022 3:29 PM
To: s22 /AU
Cc: chc.ae
Subject: [SEC=OFFICIAL] RE: Significant Safety Issue- Pholcodine
Dear s22 ,
Thank you for your notification. Should regulatory action be taken by EMA in relation to the issue, the TGA should be notified.
The TGA will be in touch should we require anything further.
Kind regards,

s22
s22
Medicines and Vaccines Investigation and Surveillance
Pharmacovigilance Branch
Email: s22 @health.gov.au

Therapeutic Goods Administration
Australian Government, Department of Health and Aged Care
PO Box 100
Woden ACT 2606
www.tga.gov.au

From: s22 /AU s22 @sanofi.com>
Sent: Tuesday, 8 November 2022 9:21 AM
To: Signal Investigation Coordinator <si.coordinator@health.gov.au>
Cc: chc.ae <chc.ae@sanofi.onmicrosoft.com>
Subject: Significant Safety Issue- Pholcodine
REMINDER: Think before you click! This email originated from outside our organisation. Only click links or open attachments if you recognise the sender and know the content is safe.
Dear Sir/Madam,
In alignment with the pharmacovigilance responsibilities of medicine sponsors, Sanofi Aventis Healthcare Pty. Ltd wants to inform the TGA of a Significant Safety Issue related to our product Pholcodine Monohydrate.
Significant Safety Issue- "Pholcodine and cross sensitivity to neuromuscular blocking agents"
Background Information-
The Signal originated from a CMDh conclusion of a PRAC request regarding pholcodine and ***agreed with the scientific conclusions made by PRAC*** in its assessment report (PSUSA/00002396/202105) for pholcodine.
The regulatory body concluded that "*In light of the available data on the risks of IgE-mediated sensitization and subsequent cross-sensitivity to neuromuscular blocking agents (NMBAs) from the literature, the PRAC believes it cannot exclude a causal relationship between pholcodine and cross-reactivity to NMBAs. The PRAC concluded that the product information for pholcodine-containing medicinal products should be amended by consequence.*
The CMDh considered that the ***benefit - risk ratio of the medicinal products containing pholcodine is unchanged subject to the proposed changes to the information*** on the medicine.
Important Milestones on the topic of Pholcodine and NMBA sensitization:

2021	Australian author Sadleir et al published results of their study conducted in Western Australia to test the hypothesis that ob risk factor for NMBA anaphylaxis, independent of differences in pholcodine consumption. The study concluded that pho consumption is also a risk factor, and this is consistent with the pholcodine hypothesis
Jun 22	Preliminary study report of PASS ALPHO was received by ANSM from sponsor– Final report expected by Sep 22 France initiated urgent union procedure under article 107i of Directive 2001/82/EC and referred to PRAC which is reque provide recommendations.
Sep 2022	***EMA has started a review*** of medicines that contain pholcodine following concerns that their use may put people at ri developing anaphylactic reactions (a sudden, severe and life-threatening allergic reaction) to certain medicines called neuro blocking agents (NMBA). ***The PRAC will now review the results of the ALPHO study together with all available data*** and assess their impact on th risk balance of pholcodine-containing medicines and issue a recommendation on whether their marketing authorizations s maintained, varied, suspended or withdrawn across the EU

Sanofi currently does not have marketing authorization (MA) for pholcodine in European region, however a signal report evaluation was initiated based on the above CMDh report.

Based on review of the Sanofi global PV database, worldwide scientific literature, main reference textbooks, biological plausibility the cumulative weight of evidence is present to support a causal association between pholcodine and cross sensitization due to the use of neuro- muscular blocking agents.

This was confirmed as a validated signal and has been classified as a risk.

Thank you.

Kind Regards

s22 [redacted]
s22 [redacted]
Consumer Healthcare
Mb. s22 [redacted]
s22 [redacted]@sanofi.com
Building D, 12-24 Talavera Road
Macquarie Park, NSW 2113

sanofi

"Important: This transmission is intended only for the use of the addressee and may contain confidential or legally privileged information. If you are not the intended recipient, you are notified that any use or dissemination of this communication is strictly prohibited. If you receive this transmission in error please notify the author immediately and delete all copies of this transmission."

"Important: This transmission is intended only for the use of the addressee and may contain confidential or legally privileged information. If you are not the intended recipient, you are notified that any use or dissemination of this communication is strictly prohibited. If you receive this transmission in error please notify the author immediately and delete all copies of this transmission."

s22

From: s22 s22 @pagb.co.uk>
Sent: Wednesday, 14 December 2022 7:33 PM
To: s22
Cc: s22 ; PBPMA
Subject: RE: ALPHO study results - TGA request [SEC=OFFICIAL]
Attachments: ALPHO_Rapport Final_15092022_Redacted_PAGB.pdf

Dear s22

Good news, we got the go ahead from the sponsoring companies to share, so please find attached.

We have just redacted any personal identifiable names within the report just in case it breaks GDPR rules here in the EU. However this shouldn't make any difference to the content of the report, but if it does cause an issue let me know.

Do let me know if there is anything else that you need.

I do also plan to share this with my colleagues in the Australian Consumer Healthcare Trade Association.

Thanks

Kind Regards

s22

s22

Email s22 @pagb.co.uk
Mobile s22

PAGB The Consumer Healthcare Association

From: s22 @health.gov.au>
Sent: 12 December 2022 01:08
To: s22 @pagb.co.uk>
Cc: s22 @health.gov.au>; PBPMA s22 @Health.gov.au>
Subject: RE: ALPHO study results - TGA request [SEC=OFFICIAL]

Thank you for your response s22 ,

I understand this request is somewhat complex due to the ownership of the sponsors involved. I would greatly appreciate it if you could provide a coordinated response from the sponsors. Please let me know if you have any issues and I can reach out to individual sponsors as needed.

Kind regards

s22 [redacted]
s22 [redacted]
Medicines and Vaccines Investigation and Surveillance

Medicines Regulation Division | Health Products Regulation Group
Pharmacovigilance Branch
Australian Government Department of Health and Aged Care
T: s22 [redacted] | E: s22 [redacted]@health.gov.au
PO Box 100, Woden ACT 2606, Australia

*s22 [redacted] s2 [redacted]@health.gov.au) is s22 [redacted]

I acknowledge the Traditional Custodians of Australia and their continued connection to land, sea and community. I pay my respect to all Elders past and present.

From: s22 [redacted]@pagb.co.uk>
Sent: Friday, 9 December 2022 3:13 AM
To: s22 [redacted]@health.gov.au>
Cc: s22 [redacted]@health.gov.au>; PBPMA s22 [redacted]@Health.gov.au>
Subject: RE: ALPHO study results - TGA request [SEC=OFFICIAL]

Dear s22 [redacted]

Thanks for reaching out. The team at MHRA mentioned they had an enquiry from another regulator about the Alpho study and I suggested that they pass on my name.

I have spoken to a couple of the licence holders who helped fund the study and they were initially happy to share, but I think on further contemplation they were a little worried, that it may need permission from all the of the companies who paid for the study. As such I was trying to work out the best way to help achieve this, as there a number of them and they are all based in Europe.

One of the companies has given me the contact names of all companies involved, so I was going to ask a member of my team to reach out to them to get a coordinated response from them. This may take a couple of days. Hopefully we will get a positive response and then I will be able to forward onto you.

An alternative way may be for me to share the names of those companies who paid for the study and you could always reach out to those that have an office in Australia to provide it to you?

To prevent delay I will get the team activated to reach out to members in Europe to ask the question, whilst you can decide which way you would like to approach it.

Thanks

Kind Regards

s22

s22
s22
Email s22 @pagb.co.uk
Mobile s22

From: s22 @health.gov.au>
Sent: 08 December 2022 09:57
To: s22 @pagb.co.uk>
Cc: s22 @health.gov.au>; PBPMA s22 @Health.gov.au>
Subject: ALPHO study results - TGA request [SEC=OFFICIAL]

Dear s22 ,

The Signal Management Team (s22) from the MHRA gave me your contact details and suggested that you may be able to assist with a request.

The Therapeutics Goods Administration in Australia is currently undertaking an urgent review of the safety of pholcodine containing medicines, following the EMA's notification of the withdrawal of pholcodine medicines (https://www.ema.europa.eu/en/news/ema-recommends-withdrawal-pholcodine-medicines-eu-market). I am thus trying to expedite the receipt of the ALPHO study results to assist in our review, would you be able to provide these to the TGA?

Thank you for any assistance you can provide.

Sincerely,

s22
s22
Medicines and Vaccines Investigation and Surveillance

Medicines Regulation Division | Health Products Regulation Group
Pharmacovigilance Branch
Australian Government Department of Health and Aged Care
T: s22 | E: s22 @health.gov.au
PO Box 100, Woden ACT 2606, Australia

s22 [redacted] @health.gov.au) is s22 [redacted]

I acknowledge the Traditional Custodians of Australia and their continued connection to land, sea and community. I pay my respect to all Elders past and present.

s22 [redacted]

From: TGA International <s22 [redacted]@health.gov.au>
Sent: Wednesday, 22 November 2023 2:06 PM
To: s22 [redacted]
Subject: FW: Urgent request for EMA documents [SEC=OFFICIAL]

Follow Up Flag: Follow up
Flag Status: Flagged

From: s22 [redacted]@ext.ema.europa.eu>
Sent: Wednesday, 21 December 2022 10:34 PM
To: TGA International s22 [redacted]@health.gov.au>; TGA International s22 [redacted]@health.gov.au>; TGA International s22 [redacted]@health.gov.au>
Cc: EMA International <EMAInternational@ema.europa.eu>; Pholcodine-1521 <Pholcodine-1521@ema.europa.eu>; TGA International s22 [redacted]@health.gov.au>
Subject: RE: Urgent request for EMA documents [SEC=OFFICIAL]

Hi s22 [redacted],

I am glad to see from other emails that you have successfully received the documents sent today in a new Eudralink package protected by password.
Please follow the instructions by my colleague s22 [redacted] and delete the separate email sent with the password.

As highlighted before, please kindly note that the information is being provided under the terms of the CA between the EMA and TGA. This information, which is now being shared with you only, needs to be protected and is not to be shared with any third parties, published or reference their content without prior explicit authorisation by EMA.

Regarding the documents and pholcodine assessment overall, please do not hesitate to contact us for any question or clarification.

Thank you.
Kind regards,
s22 [redacted]

s22 [redacted]

s22 [redacted]

European Medicines Agency
Domenico Scarlattilaan 6 | 1083 HS Amsterdam | The Netherlands
Telephone s22 [redacted]
s22 [redacted]@ext.ema.europa.eu | www.ema.europa.eu

Follow us:

From: TGA International s22 [redacted]@health.gov.au>
Sent: Tuesday, 20 December 2022 23:28

To: s22 @ext.ema.europa.eu>; s22 s22 @health.gov.au>; s22 s22 @health.gov.au>
Cc: EMA International <EMAInternational@ema.europa.eu>; Pholcodine-1521 <Pholcodine-1521@ema.europa.eu>; s22 s22 @health.gov.au>
Subject: RE: Urgent request for EMA documents [SEC=OFFICIAL]

Hi s22

If you could send me a copy of the actual documents on this occasion that would be fantastic. Thank you.

Kind regards

s22
TGA International

Therapeutic Goods Administration

T: 1800 020 653 | E: s22 @health.gov.au
PO Box 100, Woden ACT 2606

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s22 @ext.ema.europa.eu>
Sent: Wednesday, 21 December 2022 1:47 AM
To: TGA International s22 @health.gov.au>; TGA International s22 @health.gov.au>
Cc: EMA International <EMAInternational@ema.europa.eu>; Pholcodine-1521 <Pholcodine-1521@ema.europa.eu>; TGA International s22 @health.gov.au>
Subject: RE: Urgent request for EMA documents [SEC=OFFICIAL]

Hi s22 ,

Thank you for your reply. Hope it is sorted it out soon.

We would be happy to re-send the documents if needed. Please do not hesitate to contact me.

Please note that EMA will be closed from 23 December until 3 January 2023.

Kind regards,
s22

s22
s22

European Medicines Agency
Domenico Scarlattilaan 6 | 1083 HS Amsterdam | The Netherlands
Telephone s22
s22 @ext.ema.europa.eu | www.ema.europa.eu

Follow us:

From: TGA International s22 @health.gov.au>
Sent: Tuesday, 20 December 2022 06:17
To: s22 @ext.ema.europa.eu>; s22 @health.gov.au>
Cc: EMA International <EMAInternational@ema.europa.eu>; Pholcodine-1521 <Pholcodine-1521@ema.europa.eu>; s22 @health.gov.au>
Subject: RE: Urgent request for EMA documents [SEC=OFFICIAL]

Hi s22

I still haven't managed to get these as yet and am hopeful IT can get this sorted for me before end of week.

Kind regards

s22
TGA International

Therapeutic Goods Administration

T: 1800 020 653 | E: s22 @health.gov.au
PO Box 100, Woden ACT 2606

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s22 @ext.ema.europa.eu>
Sent: Monday, 19 December 2022 10:59 PM
To: TGA International s22 @health.gov.au>
Cc: EMA International <EMAInternational@ema.europa.eu>; Pholcodine-1521 <Pholcodine-1521@ema.europa.eu>; TGA International s22 @health.gov.au>
Subject: RE: Urgent request for EMA documents [SEC=OFFICIAL]

Dear s22 ,

Hope you are well.

Could you please let me know if you have you managed to collect the documents by now?

Thank you.
Kind regards,
s22

s22

s22

European Medicines Agency
Domenico Scarlattilaan 6 | 1083 HS Amsterdam | The Netherlands
Telephone s22
s22 @ext.ema.europa.eu | www.ema.europa.eu

Follow us:

From: s22

Sent: Monday, 12 December 2022 14:32

To: TGA International s22 @health.gov.au>

Cc: EMA International <EMAInternational@ema.europa.eu>; Pholcodine-1521 <Pholcodine-1521@ema.europa.eu>; s22 @health.gov.au>

Subject: RE: Urgent request for EMA documents [SEC=OFFICIAL]

Hi s22 ,

Apologies, we do not have encrypted email connection with TGA so we are only allowed to use Eudralink.

Last Friday, I was informed of problems with received Eudralink packages by external users. The instructions were to ask users to check the spam/junk folder and mark emails from no-reply@ema.europa.eu as 'not spam' or 'safe', and to liaise with your IT department to whitelist the eudralink1.ema.europa.eu and *.ema.europa.eu domains.

In case it is helpful, please transmit these instructions to your IT department, Hope the issue is resolved soon. Please keep me updated.

Thank you.
Kind regards,
s22

s22

s22

European Medicines Agency
Domenico Scarlattilaan 6 | 1083 HS Amsterdam | The Netherlands
Telephone s22
s22 @ext.ema.europa.eu | www.ema.europa.eu

Follow us:

From: TGA International s22 @health.gov.au>

Sent: Monday, 12 December 2022 04:46

To: s22 @ext.ema.europa.eu>; s22 @health.gov.au>

Cc: s22 @ema.europa.eu>; EMA International <EMAInternational@ema.europa.eu>; s22 @ema.europa.eu>; Pholcodine-1521 <Pholcodine-1521@ema.europa.eu>; s22 @health.gov.au>; s22 s22 @health.gov.au>

Subject: RE: Urgent request for EMA documents [SEC=OFFICIAL]

Hi s22

Thank you for helping with this and we not your information sharing caveat.

Unfortunately we are unable to open documents from EudraLink until this issue is resolved with our IT. Is it possible for these to be sent to me in word or pdf?

Kind regards

s22
TGA International

Therapeutic Goods Administration

T: 1800 020 653 | E: s22 @health.gov.au
PO Box 100, Woden ACT 2606

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s22 @ext.ema.europa.eu>
Sent: Friday, 9 December 2022 3:34 AM
To: TGA International s22 @health.gov.au>
Cc: s22 @ema.europa.eu>; EMA International <EMAInternational@ema.europa.eu>; s22 @ema.europa.eu>; Pholcodine-1521 <Pholcodine-1521@ema.europa.eu>; TGA International s22 @health.gov.au>; TGA International s22 @health.gov.au>
Subject: RE: Urgent request for EMA documents [SEC=OFFICIAL]

Dear s22 ,

We have just sent the documents through our secure message system (Eudralink). Could you please confirm the receipt?

As highlighted in the message, please kindly note that the information is being provided under the terms of the Confidentiality Arrangement (CA) between the EMA and TGA. This information, which is now being shared with you only, needs to be protected and is not to be shared with any third parties, published or reference their content without prior explicit authorisation by EMA. We would like to specifically highlight to you the non-public nature of the ALPHO study report. This study has not been published yet and the study report was shared by the study authors with EMA solely for procedure purposes.

Thank you.
Kind regards,
s22

s22
s22

European Medicines Agency
Domenico Scarlattilaan 6 | 1083 HS Amsterdam | The Netherlands
Telephone s22
s22 @ext.ema.europa.eu | www.ema.europa.eu

Follow us:

From: s22

Sent: Thursday, 8 December 2022 12:06

To: TGA International s22 @health.gov.au>

Cc: s22 @ema.europa.eu>; EMA International <EMAInternational@ema.europa.eu>; s22 @ema.europa.eu>; Pholcodine-1521 <Pholcodine-1521@ema.europa.eu>; s22 @health.gov.au>; s22 s22 @health.gov.au>

Subject: RE: Urgent request for EMA documents [SEC=OFFICIAL]

Dear s22 ,

Thank you for your contact.
Please let me acknowledge the receipt of your request from the EMA procedure team. We are working internally to share with you soon the applicable document(s).

I will revert to you again once possible.

Thank you.
Kind regards,
s22

s22

s22

European Medicines Agency
Domenico Scarlattilaan 6 | 1083 HS Amsterdam | The Netherlands
Telephone s22
s22 @ext.ema.europa.eu | www.ema.europa.eu

Follow us:

From: TGA International s22 @health.gov.au>

Sent: Thursday, 8 December 2022 02:47

To: s22 @ema.europa.eu>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @ext.ema.europa.eu>

Cc: s22 @ema.europa.eu>; EMA International <EMAInternational@ema.europa.eu>

Subject: RE: Urgent request for EMA documents [SEC=OFFICIAL]

Hi s22 and s22

Thank you kindly. We await your reply s22 .

Kind regards

s22
TGA International

Therapeutic Goods Administration

T: 1800 020 653 | E: s22 [redacted] @health.gov.au
PO Box 100, Woden ACT 2606

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s22 [redacted] @ema.europa.eu>
Sent: Wednesday, 7 December 2022 7:56 PM
To: TGA International s22 [redacted] @health.gov.au>; TGA International s22 [redacted] @health.gov.au>; s22 [redacted] @ext.ema.europa.eu>
Cc: s22 [redacted] @ema.europa.eu>; EMA International <EMAInternational@ema.europa.eu>
Subject: RE: Urgent request for EMA documents [SEC=OFFICIAL]

REMINDER: Think before you click! This email originated from outside our organisation. Only click links or open attachments if you recognise the sender and know the content is safe.

Dear s22 [redacted],

I copy my colleague s22 [redacted], who leaded the procedure at EMA and who will be able to help you further

Kind regards

s22 [redacted]

s22 [redacted]
Stakeholders and Communication Division

European Medicines Agency
Domenico Scarlattilaan 6 | 1083 HS Amsterdam | The Netherlands
Telephone s22 [redacted]
s22 [redacted] @ema.europa.eu | www.ema.europa.eu | For directions, see How to find us

Follow us:

EUROPEAN MEDICI

From: TGA International s22 [redacted] @health.gov.au>
Sent: Wednesday, 7 December 2022 05:45
To: s22 [redacted] @ema.europa.eu>
Cc: s22 [redacted] @health.gov.au>
Subject: FW: Urgent request for EMA documents [SEC=OFFICIAL]

Hi s22 [redacted]

Hope you are well.

Not sure if you can help or direct me to someone who can in relation to obtaining EMA's assessment reports and results from the ALPHO study in relation to the recent announcement - EMA recommends withdrawal of pholcodine medicines from EU market | European Medicines Agency (europa.eu) to assist in the TGA's consideration of the issue?

Kind regards

s22 [redacted]
TGA International

Therapeutic Goods Administration

T: 1800 020 653 | E: s22 [redacted]@health.gov.au
PO Box 100, Woden ACT 2606

"Important: This transmission is intended only for the use of the addressee and may contain confidential or legally privileged information. If you are not the intended recipient, you are notified that any use or dissemination of this communication is strictly prohibited. If you receive this transmission in error please notify the author immediately and delete all copies of this transmission."

Classified as internal/staff & contractors by the European Medicines Agency${If.End}${If.App.PowerPoint}
${If.End}

Classified as internal/staff & contractors by the European Medicines Agency${If.End}${If.App.PowerPoint}
${If.End}

Classified as internal/staff & contractors by the European Medicines Agency${If.End}${If.App.PowerPoint}
${If.End}

Classified as internal/staff & contractors by the European Medicines Agency${If.End}${If.App.PowerPoint}
${If.End}

Classified as internal/staff & contractors by the European Medicines Agency${If.End}${If.App.PowerPoint}
${If.End}

Classified as internal/staff & contractors by the European Medicines Agency${If.End}${If.App.PowerPoint}
${If.End}

Classified as internal/staff & contractors by the European Medicines Agency${If.End}${If.App.PowerPoint}
${If.End}

01 December 2022
EMA/PRAC/831730/2022
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC assessment report

Procedure under Article 107i of Directive 2001/83/EC

Pholcodine-containing medicinal products

Procedure number: EMEA/H/A-107i/1521

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact Telephone +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Information on the procedure

1.1. Initiation of the procedure

The results of the ALPHO study showed a statistically significant link between exposure to pholcodine and the risk of perianaesthetic anaphylactic reaction related to neuromuscular blocking agents (NMBAs). ALPHO study was an imposed post-authorisation safety study (PASS) assessing the risk of anaphylaxis to NMBAs after use of pholcodine conducted as a condition of the marketing authorisations of pholcodine-containing medicinal products following a previous referral in 2011. In light of the new data from this PASS, taking into account the seriousness and the unpredictability of this risk and that pholcodine-containing medicinal products is used to treat non-life-threatening functional symptoms (non-productive cough), the French medicines agency (ANSM) was of the view that the benefit-risk ratio of pholcodine-containing medicinal products was no longer favourable and considered suspending the marketing authorisations of these products in France.

On 19 August 2022, ANSM therefore triggered an urgent Union procedure under Article 107i of Directive 2001/83/EC and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of pholcodine-containing medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

1.2. Steps taken during the procedure

Administrative information:

PRAC Rapporteur:	s22 [redacted]
PRAC Co-Rapporteur:	s22 [redacted]
Procedure Lead:	s22 [redacted]

Steps of the PRAC assessment:

An Article 107i procedure was triggered on:	19 August 2022
The procedure started on:	01 September 2022
The PRAC agreed on a list of questions (LoQ) to be addressed by the MAHs and stakeholders on:	01 September 2022
The deadline for submission of responses to the PRAC LoQ by the MAHs and stakeholders was:	26 September 2022
The rapporteur's preliminary assessment report on the MAHs and stakeholders responses to the PRAC LoQ was circulated to all PRAC members on:	28 October 2022
The co-rapporteur's preliminary assessment report on the MAHs and stakeholders responses to the PRAC LoQ was circulated to all PRAC members on:	28 October 2022
The rapporteur's updated assessment report was circulated to all PRAC members on:	21 November 2022
The co-rapporteur's updated assessment report was circulated to all PRAC members on:	21 November 2022

An oral explanation to the PRAC took place on:	28 November 2022
The PRAC issued a recommendation on:	01 December 2022

2. Scientific discussion

2.1. Introduction

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 medulla oblongata, cough centre of the central nervous system (CNS) used for treatment of cough and cold symptoms in children and adults.

Pholcodine has been used as a cough suppressant since the 1950s. In the European Union (EU), pholcodine-containing medicines are currently approved in seven EU Member states (MSs): Belgium, Croatia, France, Ireland, Lithuania, Luxembourg and Slovenia. Pholcodine-containing products are also available in Northern Ireland. Pholcodine-containing products are marketed in the EU MSs for symptomatic treatment of acute dry, non-productive cough in adults and children. Age limit for use in children varies between the authorised products with 30 months being the lowest age limit authorised. Pholcodine-containing medicinal products are available both with and without medical prescription. The products available without medical prescription have limited duration of use up to several days after which medical advice should be sought which is in line with general guidance for over-the-counter (OTC) products. A rough estimate of the cumulative exposure for all products in all EU countries combined is approximately 1 025 437 089 patient-years. The exposure is the highest in France, where the cumulative exposure is approximately 1 022 141 456 patient-years.

In 2011, an article 31 referral was initiated by the ANSM concerning a potential risk of IgE-sensitisation to NMBAs, such as atracurium, cisatracurium, mivacurium, pancuronium, rocuronium, suxamethonium and vecuronium, with pholcodine use. The referral was triggered following the publication of literature data suggesting a link between pholcodine consumption and cross sensitization to NMBAs resulting in anaphylactic reactions during anaesthesia. The published data referred mainly to Norway and Sweden, where pholcodine was no longer marketed. In France, data from spontaneous reporting suggested a 25% increase in the number of anaphylactic shocks to NMBAs in the period 2008/2009 when compared to the 2003/2004 period. This coincided with a 9% increase in the consumption of pholcodine-containing products in France between the two periods. As a consequence, ANSM changed the prescription status of pholcodine-containing medicines to prescription only and triggered an article 31 referral.

After a thorough review of available data during the referral procedure in 2011, the Committee for Medicinal Products for Human Use (CHMP) established that the evidence of a link between pholcodine use and NMBA-related anaphylaxis was circumstantial, not entirely consistent and not supportive of a conclusion that there was a significant risk of cross-sensitisation to NMBAs and subsequent development of anaphylaxis during surgery. However, the CHMP also concluded that further investigation on the possibility of an association between pholcodine use and NMBA-related anaphylaxis was needed. As an outcome of this referral, the conduct of a PASS (post-authorisation safety study) was imposed.

Meanwhile, in 2021, an Australian team (Sadleir et al. 2021) published the results of a monocentric study conducted in Western Australia that compared a group of patients with anaphylaxis to NMBAs (i.e. rocuronium and vecuronium) to a group of patients who had anaphylaxis to cefazolin. The results highlighted the role of obesity as a risk factor for NMBA anaphylaxis and showed that pholcodine consumption was associated with a very significant risk of anaphylaxis to NMBA muscle relaxants. This

study was assessed during the Periodic Safety Update Report single assessment (PSUSA) procedure of pholcodine finalised in 2022 (PSUSA/00002396/202105). As an outcome, notwithstanding the different anaesthesia practices and thus the fact that the results from the Australian study could not be fully extrapolated to the EU, the PRAC considered that a causal relationship between pholcodine and cross-reactivity to NMBAs could not be ruled out and recommended, while waiting for the results of the ALPHO study, to update the product information of all pholcodine-containing products (including fixed dose combinations) to warn patients and healthcare professionals (HCPs) that cross-reactivity leading to serious allergic reactions (anaphylaxis) have been reported between pholcodine and NMBAs.

The preliminary results of the ALPHO study, the imposed post-authorisation safety study (PASS) assessing the risk of anaphylaxis to NMBAs after use of pholcodine conducted as a condition of the marketing authorisations of pholcodine-containing medicinal products following the previous referral in 2011 were received by ANSM on 30 June 2022. The study results showed a statistically significant link between exposure to pholcodine and the risk of perianaesthetic anaphylactic reaction related to NMBAs.

Based on these new data which are consistent with the Australian study from Sadleir et al, the ANSM considered the hypothesis that pholcodine consumption is likely associated with a risk of unpredictable perianesthetic NMBA-related anaphylactic reaction, as confirmed. Even if the Australian study has shown that pholcodine consumption could be a risk factor of NMBA anaphylaxis, the results of this monocentric study could not be fully extrapolated to the EU due to different anaesthesia practices. The ALPHO study was imposed after the 2011 referral as a condition of the marketing authorisation for the EU, and provided more robust results as per the methodology (multicentric study conducted in the EU in a significant number of patients).

In light of the new data from the PASS, taking into account the seriousness and the unpredictability of this risk and that pholcodine-containing medicinal products is used to treat non-life-threatening functional symptoms (non-productive cough), the ANSM was of the view that the benefit-risk ratio of pholcodine-containing medicinal products was no longer favourable and considered suspending the marketing authorisations of these products in France.

After the start of the urgent Union procedure under Article 107i, pholcodine-containing products have been suspended in three EU MSs: France, Belgium and Luxembourg. Additionally, the final study results were received by ANSM on 15 September 2022.

The PRAC considered all available data, including the results of observational studies (including the ALPHO study), literature data, post-marketing case reports as well as responses submitted by the MAHs and the submissions by the stakeholders. A summary of the most relevant information is included below.

2.2. Data on the risk of anaphylaxis to NMBAs

2.2.1. PASS results (ALPHO)

The post-marketing case-control ALPHO study[1] was conducted in France (24 centers) as per the recommendation of the CHMP by collaboration of fourteen MAHs. Enrolment started in 2014 and finished in July 2020 but the results were not available in 2021 due to some accumulated delays including slow recruitment rates over the years and later the coronavirus disease pandemic (COVID-19). The results were received by ANSM in 2022.

[1] https://clinicaltrials.gov/ct2/show/NCT02250729, accessed on 11/10/2022

Methods

The primary objective of the ALPHO study was to investigate an association between pholcodine exposure and the risk of perianaesthetic anaphylactic reaction related with NMBA by comparing a group of patients who experienced a anaphylactic reaction at anaesthetic induction (case patients) to a group of patients anaesthetized with NMBA injection who did not experience a perianaesthetic anaphylactic reaction (control patients) matched (ratio 2:1) on age, gender, NMBA category, time of anaesthesia, and geographic region. The secondary objectives of the study were:

- to compare anti-pholcodine IgE, anti-ammonium IV IgE and total IgE levels between the case and control groups;
- to study the correlation between exposure to pholcodine in cases and controls, by means of a patient self-questionnaire on the one hand and, on the other hand, by a computerized drug history, supplemented by pharmaceutical file, if applicable;
- to study the impact of taking 1, 2 or 3 information sources in order to estimate pholcodine exposure;
- to study the association between exposure to pholcodine and the presence/levels of pholcodine-specific IgE, reflecting sensitisation to pholcodine;
- to study NMBA and pholcodine cross-sensitisation by testing skin reactions to pholcodine in case patients allergic to (at least) one NMBA;
- to compile a biological collection to study the predictive risk factors associated with immediate allergies.

The following inclusion criteria was followed for case and control patients:

Case Patients:

- Man or woman, ≥ 2 years old.
- Went to an allergy-anaesthesia consultation between 6 to 12 weeks (approximately) following the occurrence of a peranaesthesic anaphylactic reaction during the introduction of anaesthesia with the administration of NMBA(s).
- Given their consent (consent from both parents for a minor child).
- Affiliated to social security regime or beneficiary.
- Able to answer a questionnaire regarding medication history.
- Having a clinical state compatible with carrying out skin tests (absence of a dermatological or psychiatric illness, etc.).
- Stopped any anti-histamine treatment for at least 8 days.

Control Patients:

- Man or woman, ≥ 2 years old.
- Patient anesthetized in a control recruitment centre.
- Having undergone anaesthesia with an NMBA injection without the occurrence of a peranesthesic anaphylactic reaction, regardless of their medical background.
- Given their consent (consent from both parents for a minor child).

- Affiliated to a social security regime or beneficiary.
- Able to answer a questionnaire regarding medication history.

Pholcodine exposure in the 12 months prior to anaesthesia was measured through a self-reported questionnaire, patient's medical history and patient's electronic pharmaceutical file.

Results

The study included a total of 937 patients for 167 cases and 334 controls. Women represented 55.1% of the matched population. This is in line with the available French data that indicates that allergy to NMBAs is more common in women than men, with three of four reactions occurring in females (Mertes, 2011). The mean age was 56 years old (SD=13.1) in cases and the mean age was 57 years old (SD=15.7) in controls. This is also in line with data indicating that perioperative anaphylaxis occurs in children less frequently than in adults (Wakimoto, 2021). The mean BMI was 27.4 (SD=8.2) in cases and 27.4 (SD=7.3) in controls. Regarding pholcodine exposure, 79 (47.3%) cases and 67 (20.1%) controls had been exposed to pholcodine within 12 months before inclusion. No case or control had a known allergy to pholcodine. Of note, 33 (19.8%) cases and 18 (5.4%) of controls reported a current or previous occupation exposed to quaternary ammoniums (hairdressing or cleaning/maintenance). In addition, 150 (89.8%) cases and 309 (92.5%) controls had already undergone surgery before inclusion.

The primary results showed a statistically significant link between use of pholcodine during the 12 months preceding anaesthesia and risk of perianesthetic anaphylactic reaction related to NMBAs (OR adjusted=4.2 CI 95% [2.5; 6.9][2]). Professional exposure to quaternary ammoniums ($p<10^{-4}$) and history of hepatogastrointestinal disorders (p=0.004) were also associated with the risk of a perianaesthetic anaphylactic reaction related to a NMBA.

The study analysed the concentrations of IgE anti-pholcodine, IgE anti-quaternary ammoniums and total IgE of cases and controls. An increase of pholcodine IgE and total IgE was hypothesized after pholcodine exposure, but this hypothesis was not verified in study population, possibly because of small number of patients, subgroup analysis and thus lack of statistical power, meaning that IgE levels obtained in this study cannot be used to predict an allergy reaction to NMBA. Specific IgE antibodies to quaternary ammonium and pholcodine showed a good performance to discriminate case patients from controls. Specific IgE antibodies to quaternary ammonium and pholcodine results provided a good negative predictive value to reasonably rule out NMBA anaphylactic risk when specific IgE antibodies are undetectable. Conversely, the positive predictive value was very low, meaning that the presence of specific IgE could not allow to identify a population at risk with sufficient precision. Significant correlations were seen between pholcodine and quaternary ammonium IgE.

Most patients who have experienced an anaphylactic shock to NMBAs had positive skin tests for pholcodine, but there was no difference in these results between the exposed and unexposed to pholcodine. The study authors reported that this may indicate either that Pholcodine is irritating or that there is frequent cross-reactivity with NMBAs.

2.2.2. Literature

Literature was screened to identify available evidence about pholcodine and risk of NMBA cross-reactivity. Several publications can be found on the topic of pholcodine hypothesis, including discussion about the mechanism, influence of other substances with quaternary ammonium ions found in

[2] The OR value calculated and presented in preliminary study result and in the notification of the procedure under Article 107i is different from the final result presented in this report.

household products or to which certain professions such as hairdressers and cleaners are exposed to and description of the effect of pholcodine withdrawal from the Norwegian market.

Description of individual studies

1. Florvaag et al, 2005

In 2005, Florvaag et al. studied 300 sera of 'allergies' and 500 blood donors in Bergen and Stockholm, which were tested for IgE antibodies to morphine and suxamethonium and the results were compared to those of 65 patients from Bergen with documented anaphylaxis to NMBA. In addition, 84 different household chemicals were tested, by IgE antibody inhibition, for suxamethonium and morphine. The authors reported that IgE-sensitization to suxamethonium, morphine and pholcodine was detected in Norway but not in Sweden. Of the anaphylactic, 65-68% were sensitized to morphine or pholcodine but only 39% to suxamethonium. The authors indicated that a possible explanation was the unrestricted use of cough mixtures containing morphine derivatives in Norway.

2. Florvaag et al, 2006

In 2006, Florvaag et al. conducted a pilot study to explore the effect of exposure to cough syrup and environmental chemicals containing pholcodine, morphine and suxamethonium related allergenic structures on IgE production in IgE-sensitized and non-sensitized individuals,. Serum concentrations of IgE and IgE antibodies to pholcodine, morphine and suxamethonium allergens were followed after intake of cough syrup, or exposure to confectionary and other household chemicals containing various amounts of substances cross-reacting with pholcodine, morphine and suxamethonium. The results indicated that cough syrup containing pholcodine gave, in sensitized individuals, within 1-2 weeks, an increase of IgE of 60-105 times and of IgE antibodies to pholcodine, morphine and suxamethonium in the order of 30-80 times. The tested confectionary did not have any similar stimulating effect but seemed to counteract the expected decrease of IgE. No effect was seen in nonsensitized individuals. The pholcodine stimulated IgE showed a nonspecific binding to ImmunoCAP with common allergens and glycine background ImmunoCAP that was up to 10-fold higher than that of monomeric myeloma-IgE at twice the concentration. The authors concluded cough syrups containing pholcodine have a IgE boostering effect in persons IgE-sensitized to pholcodine, morphine and suxamethonium related allergens. Household chemicals containing such allergenic epitopes seemed capable of some, minor, stimulation.

3. Harboe et al, 2007

Harboe et al. conducted a randomized controlled trial to explore the effect of pholcodine exposure on IgE in a population with previously diagnosed IgE-mediated anaphylaxis towards NMBAs. Seventeen patients were randomized to 1 week's exposure with cough syrup containing either pholcodine or guaifenesin. The primary variables serum IgE and IgE antibodies towards pholcodine, morphine and suxamethonium were measured before and 4 and 8 weeks after start of exposure. The results showed that patients exposed to pholcodine had a sharp rise in levels of IgE antibodies towards pholcodine, morphine and suxamethonium, the median proportional increases 4 weeks after exposure reaching 39.0, 38.6 and 93.0 times that of the base levels respectively. Median proportional increase of IgE was 19.0. No changes were observed in the guaifenesin group. The authors concluded that serum levels of IgE antibodies associated with allergy towards NMBAs increase significantly in sensitized patients after exposure to cough syrup containing pholcodine.

- Johansson et al, 2009

In 2009, Johansson et al. published a report indicating that pholcodine caused anaphylaxis in Sweden 30 years ago. Pholcodine was marketed in Sweden during the 1970s and 1980s. Stored serum samples collected from patients with an IgE-mediated allergy during the period 1970-1999 were tested for IgE

antibodies to morphine, pholcodine and suxamethonium. The accumulated number of reported cases of anaphylaxis was high in the 1970s. The percentage of sera with antibodies to pholcodine and morphine dropped from the 1970s to the 1990s, although the pattern was less clear with suxamethonium. No case was reported after 1990 when pholcodine was no longer on the market. The authors concluded at the time of the publication that the pholcodine hypothesis is strengthened, and thus a general, global withdrawal of all drugs containing pholcodine needed to be seriously considered, as morbidity would be reduced and lives saved from the reduction or disappearance of anaphylaxis to NMBA.

4. Johansson et al, 2010

In 2010, Johansson et al. published results of the study that aimed to test, on a multinational level, the pholcodine hypothesis, i.e. that the consumption of pholcodine-containing cough mixtures could cause higher prevalence of IgE antibodies to pholcodine, morphine and suxamethonium. National pholcodine consumptions were derived from the United Nations International Narcotics Control Board database. IgE and IgE antibodies to pholcodine, morphine, suxamethonium and P-aminophenyl-phosphoryl choline were measured in sera from atopic individuals collected in nine countries representing high and low pholcodine-consuming nations. Results showed a significant positive association between pholcodine consumption and prevalence of IgE-sensitization to pholcodine and morphine, but not to suxamethonium and and P-aminophenyl-phosphoryl choline, as calculated both by exposure group comparisons and linear regression analysis. The Netherlands and the USA, did not have pholcodine-containing drugs on the markets, although the former had a considerable pholcodine consumption. Both countries had high figures of IgE-sensitization. The authors concluded that this international prevalence study additionally supported the pholcodine hypothesis and, consequently, that continued use of medicines containing the substance would need to be questioned.

5. Chalabianloo et al, 2010 (conference abstract)

Chalabianloo et al. reported in 2010, as a conference abstract, the results of their study that aimed to describe the clinical characteristics of patients with suspected drug hypersensitivity. The medical records of 20 consecutive patients with suspected drug hypersensitivity, enrolled from a large retrospective study designed to include about 400 patients consulted in a Norwegian Allergy Centre, were investigated with respect to history, skin tests and serology. Among results, anaphylaxis was reported in 10 patients, and 45% of the reactions occurred within 1 hour after taking the drug. Total serum IgE was increased (> 120 KU/L) in 40% and serum ECP was increased (> 22.0 mug/L) in 20% of patients. 3 patients had antigen-specific IgE antibody concentration above 0.35 KU/L (2 to penicillin and 1 to morphine/pholcodine).

6. Florvaag et al, 2011

This study aimed to describe the effects of withdrawal of pholcodine on IgE, IgE-antibodies and reported frequencies of anaphylaxis to NMBAs. Three hundred sera from supposedly allergic patients sampled yearly through 2006 to 2010 were analysed for IgE antibodies to pholcodine, suxamethonium and morphine. Furthermore, IgE and preliminary reports from the Norwegian Network for Anaphylaxis under Anaesthesia were monitored. Results showed that pholcodine exposure was associated with IgE sensitization to pholcodine, morphine and suxamethonium. However, after withdrawal, within 1 year, antibody prevalence to pholcodine and suxamethonium fell significantly from 11.0% to 5.0% and from 3.7% to 0.7%, respectively. At 3 years, suxamethonium had fallen to 0.3%, pholcodine to 2.7% and morphine to 1.3%. By 2 years, the prevalence of elevated IgE was significantly reduced. After 3 years, the incidence of reported suspected anaesthetic anaphylaxis fell significantly, both the total number, the reactions related to NMBAs and those with IgE antibodies to suxamethonium. The authors concluded that withdrawing of pholcodine lowered significantly within 1-2 years levels of IgE and IgE antibodies to pholcodine, morphine and suxamethonium, and, within 3 years, the frequency of NMBA

suspected anaphylaxis. The authors stated that results strengthened the pholcodine hypothesis considerably and equally the need to question the existence of cough depressants containing pholcodine.

7. Clarke et al, 2011 (conference abstract)

In a conference abstract presented in 2011, Clarke et al. presented a ten-year retrospective study of anaphylaxis caused by muscle relaxants in Western Australia. All cases of NMBA anaphylaxis between 2000 and 2010 were reviewed. The results showed there were 75 cases of anaphylaxis in the study period. In the same time, there were 1,816,437 general anaesthetics, 35 to 45% of which included a NMBA. The risk of anaphylaxis in Western Australia from a NMBA per exposure is 1/8500 to 1/10,900. During the study period, rocuronium was used on average 1.42 times more than vecuronium. Cross-reactivity was absent in 25% of cases. In one case cross-reactivity was demonstrated to all NMBA tested. Suxamethonium and rocuronium most commonly cross-reacted whereas cisatracurium did so the least. There were no deaths, but two cases were associated with residual cerebral dysfunction. The authors discussed that anaphylaxis rates to NMBA vary from 1/5200 - where pholcodine is freely available - to 1/200,000 where it is not. In Western Australia, the rate was consistent with the former. Cross-reactivity was not entirely predictable on the basis of structure. There was insufficient data to make any judgment about relative risk of allergic reactions with those neuromuscular blocking agents rarely used, but the cross-reactivity rates would support the belief that suxamethonium is particularly allergenic. When comparing the usage of rocuronium and vecuronium with their proportion of the total number of cases of neuromuscular blocking agent anaphylaxis, a relative risk index of 2.89 could be calculated. This is supported in the cross-reactivity data where rocuronium is the second most likely drug (after suxamethonium) to skin test positive. Cisatracurium was the least likely NMBA to cross-react.

8. Johansson et al, 2012 (case series)

In this article, the authors present four case reports of anaphylaxis to atracurium in Sweden, in which none was IgE sensitised to morphine, pholcodine or suxamethonium. One case had a positive basophil test (basophil allergen threshold sensitivity) to atracurium, but was negative to the other NMBAs. Serological testing showed that two of the four patients had IgE antibodies to atracurium. The IgE binding could be completely inhibited by atracurium, but not by the other six NMBAs or by pholcodine.

9. Dong et al, 2013 (exposure to professional occupational factors)

The study aimed to investigate the prevalence of specific IgE to quaternary ammonium ions in two populations professionally exposed to quaternary ammonium compounds, in the North-Eastern France.

The authors observed a 4.6-fold higher frequency of positive IgE against quaternary ammonium ions in hairdressers, compared with baker/pastry makers and control groups. The competitive inhibition of quaternary ammonium Sepharose radioimmunoassay with succinylcholine was significantly higher in hairdressers, compared with baker/pastry makers and control groups, with inhibition percentage of 66.2 +/- 7.4, 39.7 +/- 6.0 and 43.8 +/- 9.9, respectively ($P < 0.001$). The specific IgE against quaternary ammonium ions recognized also two compounds widely used by hairdressers, benzalkonium chloride and polyquaternium-10. When considering the whole study population, hairdresser professional exposure and total IgE > 100 kU/L were the two significant predictors of IgE-sensitization against quaternary ammonium ions in the multivariate analysis of a model that included age, sex, professional exposure, increased concentration of total IgE (IgE > 100 kU/L) and positive IgE against prevalent allergens ($P = 0.019$ and $P = 0.001$, respectively). As conclusion, the authors considered that the study suggested that repetitive exposure to quaternary ammonium compounds used in hairdressing is a risk factor for NMBAs sensitization.

10. Katelaris et al, 2014

Serum samples in Australia, Japan and Republic of Korea were tested for IgE antibodies to suxamethonium, pholcodine and morphine. The prevalences of IgE-antibodies to pholcodine, morphine, and suxamethonium were 10%, 8.6%, and 4.3%, respectively, in Australia. The corresponding figures for Japan were 0.8%, 0.8%, and 1.5%, and for Korea 1.0% to pholcodine and 0.5% to morphine and suxamethonium. Of the suxamethonium-positive sera, 100% were positive to pholcodine or morphine in Australia and 0% in Japan and Korea.

11. De Pater et al, 2017

The authors conducted a six-year follow-up study on the effects of pholcodine withdrawal on IgE sensitization and anaphylaxis reporting. From 650 acute consecutive reports (2005-2013) to the Norwegian Network for Anaphylaxis under Anaesthesia, total number of reports on suspected anaphylactic reactions, number of reactions where NMBAs were administered, number of reactions where serum IgE antibodies (≥0.35 kUA /l) to suxamethonium and pholcodine were present at time of reaction and anaphylaxis severity grades were retrieved. In addition, NMBA sales and prevalence of IgE sensitization to pholcodine and suxamethonium among 'allergics' were monitored. From baseline period P0 (pholcodine on the market) through the first (P1) and second (P2), three-year periods after withdrawal, significant falls in total reports ($P<0.001$) and reports with IgE antibodies to pholcodine ($P=0.008$) and suxamethonium ($P=0.001$) at time of reaction were found. Total NMBA sales in P2 were 83% of P0, and suxamethonium and rocuronium together made up 86% of sales throughout the study. Five NMBA-related anaphylactic deaths occurred during P0 and P1 and, however, none during P2. Prevalence of IgE sensitization to suxamethonium in 'allergics' fell to 0% at 4 and 5 years after withdrawal. The authors considered that the decline suggested that the Norwegian population had gradually become less IgE-sensitised and clinically more tolerant to NMBA exposure.

12. Anderson et al. 2020

The authors note that specific IgE to NMBAs is frequently examined using morphine as a marker for the substituted ammonium groups considered to be the main allergenic epitopes of NMBAs and pholcodine (a morphine derivative) has also been suggested as an effective marker for detection of specific IgE to substituted ammonium epitopes. However, considerable variation can be seen between specific IgE concentrations to morphine or pholcodine in NMBA-allergic patients. The analysis reported by the authors was undertaken to investigate these variations and the value of the pholcodine specific IgE assay in the assessment of NMBA allergic patients. A retrospective study was carried out for all patients investigated at the Royal North Shore Hospital Anaesthetic Allergy Clinic (Sydney, Australia) from June 2009 to September 2019. Standardised skin testing was performed with a panel of NMBAs including rocuronium, vecuronium, pancuronium, succinylcholine, and cisatracurium. Measurement of pholcodine and morphine specific IgE was performed for all patients. A total of 801 consecutive patients were examined. Of these, 255 exhibited positive skin test results for NMBAs (187 female, 68 male, median age 52 years). Pholcodine specific IgE concentrations were quantitatively higher than morphine specific IgE concentrations in 56% of skin test positive patients. Where patients had pholcodine specific IgE concentrations two or more times the concentration of morphine specific IgE, a significantly increased proportion had skin sensitisation to succinylcholine. The authors concluded that comparison of variation in the concentrations of specific IgE between the pholcodine and morphine substrates may provide increased information regarding which NMBAs could present a risk for future procedures, with results from the current analysis indicating that this may be of use in the assessment of risk associated with subsequent succinylcholine exposure.

13. Sadleir et al, 2021

In this study, 145 patients diagnosed with intraoperative NMBA anaphylaxis in Western Australia between 2012 and 2020 were compared with 61 patients with cefazolin anaphylaxis with respect to BMI grade, history of pholcodine consumption, sex, age, comorbid disease, and NMBA type and dose. Confounding was assessed by stratification and binomial logistic regression. Obesity (odds ratio [OR]=2.96, $\chi 2$=11.7, P=0.001), 'definite' pholcodine consumption (OR=14.0, $\chi 2$=2.6, P<0.001), and female sex (OR=2.70, $\chi 2$=9.61, P=0.002) were statistically significant risk factors for NMBA anaphylaxis on univariate analysis. The risk of NMBA anaphylaxis increased with BMI grade. Confounding analysis indicated that both obesity and pholcodine consumption remained important risk factors after correction for confounding, but that sex did not. 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). The authors concluded that obesity is a risk factor for NMBA anaphylaxis (the risk increasing with BMI grade), pholcodine consumption is an additional risk factor and rocuronium use is associated with an increased risk of anaphylaxis compared with vecuronium in this population.

14. Malvik et al, 2022

The authors reported that in Norway, from 1997 to 2007, there was a mean of 76 reports per year, and after an initial yearly increase in number of reports following the establishment of the registry, there was a mean of 87 yearly reports from 2001 to 2007. After 2007, the mean number of reports fell to 61, with stable reporting from 2009.

2.2.3. Post-marketing data

The MAHs have performed analysis of cases reported to their pholcodine-containing products and presented data in their responses. Cumulatively, there were a total of 88 cases identified in MAHs safety databases reporting PTs from the SMQ Anaphylactic reaction where pholcodine-containing medicinal product(s) is a suspected or interacting medicinal product with relation to NMBA. Additionally, three MAHs performed searches for similar cases in the EudraVigilance database. Provided details about cases were analysed by the PRAC to assess whether cases concern safety issue of interest (anaphylaxis to NMBAs with previous exposure to pholcodine). Cumulatively there were 24 cases from either MAHs databases or EudraVigilance. It was not possible to exclude duplicates since not all MAHs provided case numbers. 14 cases were serious, 1 was non-serious, while other 9 were missing data about seriousness. 3 cases reported fatal outcome, 7 cases reported outcome as recovered or recovering, while in other 14 cases outcome was unknown. Time between pholcodine exposure and onset of anaphylaxis ranged between 2 and 3 months in cases where it was reported.

Overall, analysed cases from either MAHs databases or EudraVigilance raise suspicion regarding association between pholcodine and anaphylaxis to NMBAs. Most of the ICSRs analysed, based on their Eudravigilance numbers where it was available, originated either from France or Australia where the two recent studies (ALPHO and Sadleir et al 2021.) were performed. Therefore, cases presented in the MAHs' reviews could be result either of ICSRs originating from published medical literature or due to raised awareness amongst medical professionals and therefore increased spontaneous reporting rate. It is also possible that most of these patients (and suspected ADRs) are already included in results from respective studies which are discussed in this report.

2.2.4. Discussion on the risk of anaphylaxis to NMBAs

Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in airway,

breathing and/or the circulation, and may occur without typical skin features or circulatory shock being present (Cardona, 2020). Perioperative anaphylaxis, including anaphylaxis to NMBAs, is a serious and life threatening medical condition which is rare (1/10.000 anaesthesia procedures) but with relatively high mortality (4-6%) despite immediate access to treatment in the anaesthetic department. Perioperative anaphylaxis can occur via IgE-dependent mechanism, which account for approximately 60 percent of perioperative anaphylaxis, non-IgE-dependent immunological mechanisms (mediated by IgG or IgM antibodies or by antigen-antibody complexes and complement) or nonimmunologic mechanisms involving direct release of histamine and other mediators from mast cells and basophils (Levy, 2022).

The most common reported cause of anaphylaxis during general anaesthesia or postoperatively are NMBAs, which are responsible for 60% to 70% of episodes of anaphylaxis occurring during this period (Mali, 2012). NMBAs are usually administered during anaesthesia to facilitate endotracheal intubation and/or to improve surgical conditions. NMBAs may decrease the incidence of hoarseness and vocal cord injuries during intubation, and can facilitate mechanical ventilation in patients with poor lung compliance. The NMBAs most commonly implicated are succinylcholine (known as suxamethonium), rocuronium, atracurium, vecuronium, pancuronium, mivacurium, and cisatracurium. Allergy to NMBAs is more common in women than men, with three of four reactions occurring in females (Levy, 2022). The rate of NMBA anaphylaxis shows marked geographical variation in patients who have had no known prior exposure to NMBAs (Brusch, 2014) .

NMBAs can cause anaphylaxis through both IgE-mediated and nonimmunologic, direct mast cell activation. There may be a specific receptor on mast cells activated by NMBAs as well as other drugs, such as fluoroquinolones and vancomycin. This receptor is designated Mas-related G-protein coupled receptor X2 (MRGPRX2) and has the capability of binding to a variety of ligands, resulting in mast cell activation clinically resembling an immune response. Reactions resulting from IgE-mediated allergy generally are less common, although usually more severe, than reactions due to other mechanisms. IgE sensitization is believed to occur due to cross-reactive tertiary or quaternary ammonium groups found in both NMBAs and a variety of topical cosmetics and personal products, as well as certain medicines, such as pholcodine. These ammonium groups are highly immunoreactive, multivalent epitopes, which can induce specific IgE antibodies. Sensitization through exposure to nonmedication agents may explain why allergic reactions to NMBAs occasionally occur upon initial exposure (Ledford, 2022).

The evaluation of suspected perioperative anaphylaxis involves a verification that the reaction was clinically consistent with anaphylaxis, clinical history, review of records of the event, analysis of laboratory tests obtained at the time, and skin testing or in vitro serum-specific IgE testing if the reaction was believed to be IgE-mediated. Skin testing and challenge procedures to identify drug allergy should be performed by allergy specialists trained in the safe performance and accurate interpretation of these tests and manoeuvres (Ledford, 2022).

Pholcodine is an opiate with central antitussive and it is thought to induce immunologic stimulation in exposed individuals. The consequence of such IgE sensitisation in general is not known, but this raised the concern that patients may be put at risk of allergic reactions and even anaphylactic reaction to other substances, particularly allergens with a quaternary ammonium ion e.g. NMBAs. This theory is known as the pholcodine hypothesis. Throughout the years several studies have been published by the same group of authors (Florvaag et al) investigating the increased prevalence of IgE antibodies to pholcodine, morphine and suxamethonium, and ultimately higher incidence of IgE-mediated anaphylactic reactions to NMBAs in Norway. However, while these studies demonstrated potential effect of pholcodine use on the occurrence of NMBA related anaphylaxis, it should be noted that the studies rely on the number of spontaneously reported cases of NMBA related anaphylaxis. The

observed decrease in the number of reported cases of NMBA-related anaphylaxis could be results of less reporting, changes to clinical practice, change in type of NMBA use, etc.

The most relevant publication from the literature is that of Sadleir et al (2021). In this case-control study from Australia, authors described that obesity is a risk factor for NMBA-related anaphylaxis and the risk increases with BMI grade. The authors also concluded that consumption of pholcodine is an independent and statistically significant risk factor for NMBA anaphylaxis (OR = 12.0; CI = 3.75-43; p-value < 0.001). However, several limitations in this study were identified, such as representativeness of patient population, recall bias to pholcodine exposure, possible misclassification of cases, different use of NMBAs than in the EU and power of the study. Nevertheless, the data from this study which was assessed in a separate regulatory procedure (PSUSA assessment) led to the inclusion of warning in the section 4.4 of the summary product characteristics (and section 2 package leaflet) of pholcodine-containing medicinal products and establishing of a potential risk.

The findings of the ALPHO study add to the cumulating evidence that there is a plausible causal relationship between pholcodine use and NMBA-related anaphylaxis and pholcodine is an important risk factor for NMBA-related anaphylaxis. The study was specifically designed to investigate an association between pholcodine exposure and the risk of perianaesthetic anaphylactic reaction related with NMBAs following the referral procedure 2011. Additionally, ALPHO was a multicentric study conducted in the EU (France) with collection of data from a large and significant number of patients and therefore considered representative of the EU population. The primary results showed a statistically significant link between use of pholcodine during the 12 months preceding anaesthesia and risk of perianesthetic anaphylactic reaction related to NMBAs (OR adjusted=4.2 CI 95% [2.5; 6.9]).

The main uncertainty about the risk observed is the detection of another factors associated with the risk of a peranesthesic anaphylactic reaction related to a NMBA, such as professional exposure to quaternary ammoniums. Significantly, more patients with professional exposure to quaternary ammoniums were included into case vs. control populations (approx. 5.4 vs. 19.8%, p < 0.0001). In the study, the case vs. control patients were paired according to age, sex, the NMBA type used, the amount of time passed since the anaesthesia and the geographical region. Additionally, in order to limit confounding, cases were matched to controls on sex, category of NMBA injected, geographic area and period of anaesthesia and the association between pholcodine exposure and risk of anaphylactic reaction was notably adjusted based on history of surgery and occupational exposure to quaternary ammoniums (cleaners, hairdressers). Nonetheless, the factor that was found to dramatically increase the risk (OR 6.07) of the peranesthesic anaphylactic reaction related to a NMBA - professional exposure to quaternary ammoniums – was significantly prevalent in matched case population, comparing with control population. There are some other study limitations, such as weak agreement between the results of the self-administered questionnaires and the medicinal histories, long period before a surgical procedure to be taken into account in regards to pholcodine use (12 months), which meant that patient could forget the fact of using pholcodine-containing medicinal product or, in opposite, state that pholcodine-containing medicinal product was used by mistaking it with another product.

From the review of the study, question arises whether pholcodine exposure was adequately established, both for controls and cases. Patients needed to recall their use of pholcodine in the period of one year, i.e. use of pholcodine could not be easily identified via prescription/dispensing data. The period of one year based on diminishing levels of IgE is acceptable, although it is noted that it might introduce a significant recall bias. Overall, when assessing pholcodine exposure, a small overlap between pholcodine exposure confirmed by self-administered questionnaire and pharmacy dispensary data was achieved. For only 21 exposed patients, both sources were positive (self-administered questionnaire and the dispensing pharmacist's medical history). This could be explained, as authors

proposed, by the fact that patients used phocodine products already available at home, possibly dispensed for other family member or someone else could have given it to them. Or dispensary data was not retrieved from all pharmacies where patients could have received the medicine. Also, it could be argued that patients suffering more often from respiratory infections were likely to recall the use of pholcodine. Study authors performed evaluation of the impact of taking into account different sources of information for the estimation of pholcodine exposure (self-administered questionnaires, medical history of the dispensary pharmacist(s), electronic pharmaceutical file) on the occurrence of NMBA related anaphylaxis. In case both sources were positive, a significant association was seen (OR adjusted=11.03 CI 95% 3.09 - 39.40), however due to small number of cases the confidence interval is considered wide indicating less precision and study is underpowered.

Despite the above described limitations it is considered that, the ALPHO study was adequately designed and supports that pholcodine is identified as an independent risk factor for NMBA-related anaphylaxis.

Additionally, the PRAC noted that two concerned MAH in their responses to the PRAC LoQ concluded that the benefit-risk balance of their concerned pholcodine-containing medicinal products is no longer favourable in view of the safety data available especially regarding the risk of anaphylaxis to NMBAs, the indication of pholcodine and the existing therapeutic alternatives.

The PRAC also noted the potential use of pholcodine in the context of the treatment of dry cough in COVID-19 patients in some Member States, and considered that these patients may be at risk of NMBA-related anaphylaxis in the event of progression to a severe form of COVID-19 requiring admission of the patient to the intensive care unit.

2.2.4.1. Risk minimisation measures

Several MAHs proposed to minimise this risk through:

- Revision of the product information (PI) to include more detailed information on the possible risk of cross-sensitization with pholcodine. More specifically, new detailed wording for section 4.4 of the SmPC with two key messages was suggested: (1) clinicians should inquire patients on the exposure of pholcodine in the last 12 months, prior to procedure; (2) in case of confirmation of previous use to pholcodine containing medicinal product, then serum specific IgE antibodies to quaternary ammonium ions/pholcodine and/or skin tests should be performed, prior to procedure.
- Introduction of a contraindication for pholcodine in case of previous allergic reaction to NMBAs in section 4.3 of the SmPC.
- Change in the status of pholcodine–containing medicines to 'prescription-only'.
- Patient alert card as an additional risk minimisation measure (RMM) in order to ensure that special information regarding patient important risk to be communicated prior to any operative procedure and that patient alert card is held by patient at all times in order to reach the relevant HCP when needed.
- Direct health care professional communication (DHPC) as an additional RMM to inform HCPs of cross-sensitisation between pholcodine containing medicinal product and NMBA and the need to take certain actions and cautiously adapt their practices in relation to a previous pholcodine-containing medicinal product consumption.

To note, some MAHs have stated in their responses that any RMMs should focus on the use of NMBAs in clinical practice, rather than the use of pholcodine and suggested updating the PI of NMBAs with

information regarding possible risk of cross-sensitization with pholcodine. Additionally, some of stakeholders who provided input suggested that more detailed information regarding potential anaphylaxis should be provided in the product information of pholcodine-containing medicinal products and of NMBAs. These proposals were also acknowledged by PRAC.

Each of the RMMs proposed were discussed by PRAC and overall are not considered effective measures to reduce the risk of perianaesthetic anaphylactic reaction related to NMBAs in patients previously exposed to pholcodine. To start, inclusion of contraindication in case of previous allergic reaction to NMBA in the product information of pholcodine-containing medicinal products would not minimise the risk. Patients can develop an allergic reaction to NMBA even if not previously exposed to an NMBA. Moreover, this contraindication would not prevent an event from happening. Likewise, inclusion of warning in the product information regarding previous pholcodine use is also not considered an effective measure, since patients or HCPs, could be unaware of the use, especially in the last 12 months.

Similarly, as other measures, measure of restriction of indication (to second line treatment, for example) and change of prescription status to 'prescription-only', although trying to limit patient population using pholcodine, still do not limit the risk in the population who used or is using pholcodine. PRAC considered the restriction of the indication to a second line treatment and is of the view that pholcodine in second line treatment will reduce the usage, but not reduce the risk of perianesthetic anaphylactic reactions related to NMBAs. Thus, while restricting the indication would minimise the number of patients using pholcodine, this would not minimise the risk for the individual patient. Likewise, PRAC discussed the change of the legal status of the pholcodine-containing medicinal products to prescription-only medicines and it was similarly concluded that this measure would only limit the use of pholcodine but would not limit the risk. In addition, it is noteworthy that the ALPHO study has been conducted in France where pholcodine-containing medicinal products are available as POM since April 2011. Based on the available data, pholcodine is currently available as a prescription-only medicine in the majority of Member States where it is authorised, therefore the situation in place reflects mainly the risk associated with the use of prescription-only products.

In regard to the patient alert card, this tool is also not considered an effective measure since pholcodine is used as a short-term acute treatment. Therefore, it is not expected for the patient to hold a card months after pholcodine treatment has stopped. Additionally, as an additional RMM, a DHPC would have impact in terms of information provided but would not minimise the risk. For instance, during pre-anaesthetic interviews, even if anaesthesiologists are well informed about the risk, it will not help them in their practice as they cannot predict which patients will develop cross-sensitization and reactions to NMBA. Also, patients might not recall if they were exposed to pholcodine in the last 12 months.

On another matter, PRAC noted that from the ALPHO study, it appears that measuring the presence of specific IgE antibodies to pholcodine could not be used to establish a potential for NMBA-related anaphylaxis as a precautionary measure. Besides, it is not considered as a feasible approach in many clinical settings such as in emergency situation, in which NMBAs are frequently administered.

Lasty, risk factors that would help to be taken into account to mitigate the risk could not be identified from the existing data by PRAC. Based on current data, no other mitigations to manage the risk can be proposed (such as recommendation of more specific than a 12-month time period between pholcodine usage and anaesthesia and dose or number of treatments with pholcodine) for those exposed to pholcodine. NMBAs are usually administered during anaesthesia, also in acute conditions when it might be impossible to rapidly gather information from the patient regarding the past use of pholcodine. Also, before the planned surgery to gather this information is challenging – patients usually do not remember all medicinal products they have used. Moreover, clinically doable tests to predict

anaphylaxis with (NMBAs) after the use of pholcodine are not available. As no patient specific risk factors associated with pholcodine induced NMBA sensitization is identified, and as it is not possible to predict who will need anaesthesia in the future, any patient treated with pholcodine will potentially be at risk of perianesthetic anaphylaxis related with NMBAs.

Considering the NMBA use, and the proposals to update the PI for these products, it is important to note that 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. Additionally, investigating pholcodine use prior to anaesthesia is likely be likely to be unfeasible, as the majority of patients either will not know or will not remember that they have taken pholcodine-containing medicinal products. In addition, in a real-life situation where specialists are unable to take this factor into account in clinical practice, investigation of the pholcodine use in individual patients prior to anaesthesia is not considered to be of benefit as it will not change anaesthetic practice.

2.3. Data on efficacy

Available data on the efficacy of pholcodine is limited. A review of 9 clinical studies published in the scientific literature was conducted. Eight out of nine studies identified were conducted between 1957 and 1986. Additionally, the number of available studies that used arms with pholcodine alone and those that compared it with a placebo is low (three studies described in two manuscripts, with a total of 73 participants). Also, pholcodine was used in combination products making it not possible to attribute any observed effect solely to pholcodine. Most of the studies were not sufficiently controlled, neither with active medicinal products nor a placebo, and some were conducted with associated products. The number of subjects was often limited and there was no objective criteria and recognised cut-off point for the reduction in cough. No study has been conducted on the long-term effects of pholcodine. However, this is an intrinsic issue of pholcodine, since it is an old substance for which trials have been conducted in line with the previously applicable standards.

Clinical trials have shown the antitussive efficacy of pholcodine to be superior to that of codeine, of longer duration, with an equivalent or safer toxicity profile, and with no risk of addiction (Blanchard, 2013). The most recent study (Equinozzi 2006) showed efficacy of a 3-day course of pholcodine similar to that of dextromethorphan in the treatment of adult patients with acute, non-productive cough. Although the study has its limitations owing to the lack of a placebo control arm and the non-validated and subjective nature of the results (frequency and intensity of cough), an effect was observed soon after the treatment was administered.

All these results suggest the efficacy of pholcodine in the treatment of acute non-productive cough. In comparative studies, pholcodine appears to be at least as effective as dextromethorphan or codeine with a longer duration of antitussive action related to its pharmacokinetic properties. Also, during previous referral procedure, finalized in 2012, the CHMP concluded that the existing data, covered also within this assessment is consistent and supportive of the efficacy of pholcodine in the treatment of acute non-productive cough. As conclusion, no new efficacy data about benefits of treatment of pholcodine have been identified, therefore efficacy of pholcodine in treatment of non-productive cough is considered unchanged.

3. Stakeholders input

Written submissions were also received from stakeholders. All data submitted was considered by the PRAC in reaching its conclusions.

The stakeholders noted dry irritative cough as a potential health problem with significant impact on patient's quality of life which requires treatment with effective antitussive medications. Notably, in view of several HCPs who provided input, pholcodine is one of the most effective antitussive medicines in comparison to other medicinal products available on the market in Croatia and Slovenia with no serious adverse drug reactions reported.

Additionally, some of the stakeholders stated that more detailed information regarding potential anaphylaxis needs to be provided in the product information of pholcodine-containing medicinal products and of NMBAs. The stakeholders also consider that the risk should also be communicated wider. The update of the product information would also should also include populations at higher risk for anaphylaxis reactions (underlying diseases, exposure to environmental factors, medicinal products that modify immune response etc.), so that patients that are not at high risk of possible anaphylaxis could still benefit from pholcodine.

4. 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 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 previously mentioned referral. In terms of the overall safety profile of pholcodine, the majority of adverse drug reactions belong to gastrointestinal and psychiatric disorders, similarly as for other opioids. However, throughout the years, case reports and results from studies raised the concern that patients treated with pholcodine may be put at risk of allergic reactions and even anaphylactic reaction to other substances, particularly allergens with a quaternary ammonium ion e.g. NMBAs.

Concerning this risk, in 2011, the CHMP conducted a review and considered that the evidence of a link between pholcodine and NMBA-related anaphylaxis was circumstantial and not entirely consistent. CHMP, nevertheless, concluded that further investigation on the possibility of an association between pholcodine use and NMBA-related anaphylaxis was needed. As an outcome of the referral, the conduct of a PASS (post-authorisation safety study) was imposed. The results of such study, named ALPHO, became available in 2022 and were thoroughly assessed in the present safety review. The results from the ALPHO study showed a statistically significant link between use of pholcodine during the 12 months preceding anaesthesia and risk of perianesthetic anaphylactic reaction related to NMBAs (OR adjusted=4.2 CI 95% [2.5; 6.9]). Despite some identified study limitations, the data from this study show an association between the risk of NMBA-related anaphylaxis and previous pholcodine use that cannot be refuted by other effects or biases. Moreover, the findings of the ALPHO study add to the cumulating evidence from literature reports and previous epidemiological studies that pholcodine is an important risk factor for NMBA-related anaphylaxis. Therefore, PRAC is of the view that based on the totality of evidence a causal relationship between pholcodine use and NMBA-related anaphylaxis is considered sufficiently established.

It should be also highlighted, that despite the low number of documented cases of anaphylaxis specifically against pholcodine, perioperative anaphylaxis (including anaphylaxis to NMBAs) is a serious and life threatening medical condition which is rare (1/10.000 anaesthesia procedures) but with relatively high mortality (4-6%). Therefore, all available measures should be taken to decrease its incidence. As discussed in section 2.2.4, it is noted that a broader range of agents can induce cross-sensitization to NMBAs and cause NMBA-related anaphylaxis. In the ALPHO study, exposure to such agents was a confounding risk. The exposure to these agents, such as occupational exposure to quaternary ammonium ions for example, however may not be possible to identify nor to fully prevent or minimise. Based on the evidence reviewed, pholcodine is identified as a risk factor for NMBA-related

anaphylaxis regardless of other risk factors. Importantly, epidemiological studies indicate that numbers of perioperative anaphylaxis cases are significantly reduced after pholcodine-containing medicinal products were removed from the market. This is supported by a study conducted in Norway, when six years after withdrawal of pholcodine-containing medicinal products from the Norwegian market, the Norwegian population became significantly less IgE sensitized and clinically more tolerant to NMBAs (De Pater, 2017). These results indicate the possible impact of acting upon the pholcodine usage.

In the context of the procedure and facing the evidence reviewed and noted above, PRAC discussed potential measures which would minimise the risk of NMBA-related anaphylaxis to an acceptable level such as restriction of indication, PI updates, change to prescription-only status, patient alert card and dissemination of DHPC. Overall, the RMMs are not considered by PRAC appropriate and effective measures to reduce the risk NMBA-related anaphylaxis in patients previously treated with pholcodine to an acceptable level. In general, the RMMs discussed would increase HCPs and patient awareness of the existing risk (e.g., SmPC changes, DHPC, patient alert card) or would reduce the number of the patients using pholcodine (e.g., restriction of indication or change of legal status). However, these measures would not minimise the risk of NMBA-related anaphylaxis for individual patient exposed to pholcodine. Moreover, 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. Therefore, patients exposed to pholcodine would still be at risk of NMBA-related anaphylaxis, which is regarded as serious, unpredictable and life threatening. PRAC could also not identify measures that would allow HCPs to identify which patients treated with pholcodine will develop cross-sensitization and reactions to NMBAs. Further, the PRAC could not identify condition(s) which if fulfilled would demonstrate a positive benefit-risk balance for these products in a defined patient population. Lastly, PRAC noted that other therapeutic alternatives for treatment of non-productive dry cough are available in the EU MS, such as codeine, ethylmorphine, dextromethorphan, butamirate and others.

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

Consequently, the PRAC recommended the revocation of the marketing authorisations for pholcodine-containing medicinal products.

5. Risk Management

The Committee, having considered the data submitted in the procedure was of the opinion that no feasible and proportionate risk minimisation measure would reduce the risks to an acceptable level (see section 2.2.4.1 for details on the measures reviewed).

5.1. *Direct Healthcare Professional Communications and Communication plan*

The Committee adopted the wording of a DHPC, to inform HCP of the conclusions of the review and therefore the upcoming unavailability of pholcodine-containing medicinal products. The Committee also agreed on a communication plan.

6. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 107i of Directive 2001/83/EC for pholcodine-containing medicinal products.
- The PRAC reviewed the totality of the data available for pholcodine-containing medicinal products in relation to the risk of perianaesthetic anaphylactic reaction related to NMBAs, in writing and in an oral explanation. This included the results of observational studies (including the ALPHO study), literature data, post-marketing case reports as well as responses submitted by the MAHs and the submissions by the stakeholders.
- The PRAC considered that the data reviewed confirm an association between the use of pholcodine and the risk of perianaesthetic anaphylactic reaction to NMBAs, an unpredictable and potentially life-threatening situation.
- No specific characteristics for perianesthetic anaphylactic reaction to NMBA could be identified in patients who have been treated with pholcodine, and therefore all these patients are considered at risk. In addition, the PRAC could not identify risk minimisation measures that would be effective at reducing the risk of perianaesthetic anaphylactic reaction related to NMBAs in patients who have been treated with pholcodine-containing medicinal products.
- The PRAC therefore concluded that the risk of perianaesthetic anaphylactic reaction related to NMBAs outweighs the benefit of pholcodine in the treatment of non-productive cough, a symptomatic indication considered acute and not serious.
- Further, 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.

The Committee, as a consequence, considers that the benefit-risk balance of pholcodine-containing medicinal products is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the revocation of the marketing authorisations for pholcodine-containing medicinal products.

The proposed DHPC can be found enclosed to this report.

Enclosures

1. Direct healthcare professionals communication as agreed by PRAC on 01 December 2022.
2. Communication plan as agreed by PRAC on 01 December 2022.
3. Listing of stakeholders, including MAHs, who submitted responses to the Agency for EMEA/H/A-107i/1521.

Enclosure 3. Listing of stakeholders, including MAHs, who submitted responses to the Agency for EMEA/H/A-107i/1521.

The following stakeholders submitted responses:

MAHs
Alkaloid – INT d.o.o
Biocodex
GlaxoSmithKline Consumer Healthcare (UK) Trading Limited
GlaxoSmithKline Consumer Healthcare (Ireland) Limited
Thornton & Ross Ltd
The Boots Company Plc
Pinewood Laboratories Limited
Vemedia Manufacturing B. V.
Zambon France S.A.

Other stakeholders
Healthcare professional - General Practitioner - Slovenia
Healthcare professionals' organisation - General Practice/Family Medicine - Croatia
Healthcare professional - General Practitioner - Slovenia
Healthcare professional - General Practitioner - Slovenia
Healthcare professional - General Practitioner - Slovenia
Healthcare professional - General Practitioner - Slovenia
Healthcare professional - General Practitioner - Slovenia
Healthcare professional - Clinical Pharmacology - Croatia
Healthcare professional - Slovenia
Healthcare professional - Family Medicine - Croatia
Healthcare professionals' organisation - Respiratory diseases - Croatia
Patients' organisation – Respiratory diseases - Croatia
Healthcare professional - Otolaryngology - Head and Neck Surgery Croatia

References

Blanchard E., Tunon de Lara M., 'Quel rôle pour la pholcodine dans le traitement de la toux, en 2013 ? [New insights into the role of pholcodine in the treatment of cough in 2013?]', Therapie, Vol. 68(2), March-April 2013, p. 85-91.

Brusch A.M., Clarke R.C., Platt P.R., Phillips E.J., 'Exploring the link between pholcodine exposure and neuromuscular blocking agent anaphylaxis', Br J Clin Pharmacol. Vol. 78(1); July 2014, p. 14-23.

Cardona V., Ansotegui I.J., Ebisawa M., El-Gamal Y., Fernandez Rivas M., Fineman S., Geller M., Gonzalez-Estrada A., Greenberger P.A., Sanchez Borges M., Senna G., Sheikh A., Tanno L.K., Thong B.Y., Turner P.J., Worm M., 'World allergy organization anaphylaxis guidance 2020', World Allergy Organ J. Vol. 13(10), 100472, 30 October 2020.

Chalabianloo F., Riedel B. M., Schjøtt J., Berstad A.K.H., Florvaag E., 'Hypersensitivity reactions to drugs: A retrospective analysis of clinical characteristics of patients consulting for suspected drug hypersensitivity in an Allergy Centre in Norway' in 4th International Drug Hypersensitivity Meeting. Rome Italy, 2010.

Clarke R., 'Anaphylaxis caused by muscle relaxants in Western Australia. A ten-year retrospective', in Anaesthesia and Intensive Care. Conference: Combined Scientific Meeting of the Australian and New Zealand College of Anaesthetists and the Hong Kong College of Anaesthesiologists, 2011.

de Pater G.H., Florvaag E., Johansson S.G., Irgens Å., Petersen M.N., Guttormsen A.B., 'Six years without pholcodine; Norwegians are significantly less IgE-sensitized and clinically more tolerant to neuromuscular blocking agents', Allergy, Vol. 72(5), May 2017, p. 813-819.

Dong S., Acouetey D.S., Guéant-Rodriguez R.M., Zmirou-Navier D., Rémen T., Blanca M., Mertes P.M., Guéant J.L., 'Prevalence of IgE against neuromuscular blocking agents in hairdressers and bakers', Clin Exp Allergy, Vol. 43(11), November 2013, p. 1256-62.

Equinozzi R., Robuschi M., 'Italian Investigational Study Group on Pholcodine in Acute Cough. Comparative efficacy and tolerability of pholcodine and dextromethorphan in the management of patients with acute, non-productive cough: a randomized, double-blind, multicenter study', Treat Respir Med, Vol. 5(6), 2006, p. 509-13.

Florvaag E., Johansson S.G., Irgens Å., de Pater G.H., 'IgE-sensitization to the cough suppressant pholcodine and the effects of its withdrawal from the Norwegian market', Allergy, Vol. 66(7), July 2011, p. 955-60.

Florvaag E., Johansson S.G., Oman H., Harboe T., Nopp A. 'Pholcodine stimulates a dramatic increase of IgE in IgE-sensitized individuals. A pilot study', Allergy, Vol. 61(1), January 2006, p. 49-55.

Florvaag E., Johansson S.G., Oman H., Venemalm L., Degerbeck F., Dybendal T., Lundberg M.. 'Prevalence of IgE antibodies to morphine. Relation to the high and low incidences of NMBA anaphylaxis in Norway and Sweden, respectively', Acta Anaesthesiol Scand. Vol. 49(4), April 2005, p. 437-44.

Harboe T., Johansson S.G., Florvaag E., Oman H., 'Pholcodine exposure raises serum IgE in patients with previous anaphylaxis to neuromuscular blocking agents', Allergy, Vol. 62(12), December 2007, p. 1445-50.

Johansson S.G., Florvaag E., Oman H., Poulsen L.K., Mertes P.M., Harper N.J., Garvey L.H., Gerth van Wijk R., Metso T., Irgens A., Dybendal T., Halsey J., Seneviratne S.L., Guttormsen A.B., 'National

pholcodine consumption and prevalence of IgE-sensitization: a multicentre study', Allergy, Vol. 65(4), April 2010, p. 498-502.

Johansson S.G., Oman H., Degerbeck F., Tunelli J., Florvaag E., Nopp A., 'Anaphylaxis to atracurium - a non-QAI-dependent reaction?, Acta Anaesthesiol Scand, Vol. 56(2), February 2012, p. 262-3.

Johansson S.G., Oman H., Nopp A., Florvaag E., 'Pholcodine caused anaphylaxis in Sweden 30 years ago', Allergy, Vol. 64(5), May 2009, p. 820-1.

Katelaris C.H., Kurosawa M., Moon H.B., Borres M., Florvaag E., Johansson S.G., 'Pholcodine consumption and immunoglobulin E-sensitization in atopics from Australia, Korea, and Japan', Asia Pac Allergy, Vol. 4(2), April 2014, p. 86-90.

Ledford D.K., Perioperative anaphylaxis: Evaluation and prevention of recurrent reactions, UpToDate [Accessed 01 December 2022, from https://www.uptodate.com/contents/perioperative-anaphylaxis-evaluation-and-prevention-of-recurrent-reactions].

Levy J.H., Ledford D.K., 'Perioperative anaphylaxis: Clinical manifestations, etiology, and management', UpToDate [Accessed 01 December 2022, from https://www.uptodate.com/contents/perioperative-anaphylaxis-clinical-manifestations-etiology-and-management].

Mali S. 'Anaphylaxis during the perioperative period', Anesth Essays Res, Vol. 6(2), July-December 2012, p. 124-33.

Malvik L.B., De Pater G.H., Dahle G.O., Guttormsen A.B., 'Gender-specific decline in perioperative allergic reactions in Norway after withdrawal of pholcodine', Allergy, Vol. 77(4), April 2022, p. 1317-1319.

Sadleir P.H.M., Clarke R.C., Goddard C.E., Day C., Weightman W., Middleditch A., Platt P.R., 'Relationship of perioperative anaphylaxis to neuromuscular blocking agents, obesity, and pholcodine consumption: a case-control study', Br J Anaest, Vol. 126(5), May 2021, p. 940-948.

Sadleir, P.H., Clarke, R.C., Bunning, D., & Platt, P.R., 'Anaphylaxis to neuromuscular blocking drugs: incidence and cross-reactivity in Western Australia from 2002 to 2011', British journal of anaesthesia, 2013, Vol. 110 (6), p. 981-7.

s22 [redacted]

From: s22 [redacted]
Sent: Thursday, 23 November 2023 11:07 AM
To: s22 [redacted]
Subject: FW: OUTCOMES - Education and Social Media report – March 2023 - HPRG Exec meeting 27 February [SEC=OFFICIAL]

From: s22 [redacted]@health.gov.au>
Sent: Friday, 10 March 2023 4:18 PM
To: NOYEN, Benjamin <Benjamin.Noyen@health.gov.au>; s22 [redacted]@health.gov.au>; s22 [redacted]@Health.gov.au>
Subject: OUTCOMES - Education and Social Media report – March 2023 - HPRG Exec meeting 27 February [SEC=OFFICIAL]

Hi s22 [redacted], s22 [redacted] and s22 [redacted]

Thank you for attending HPRG Executive meeting on 27 February for the **Education and Social Media report – March 2023**.

Below are the outcomes for this item from the meeting as cleared by Dep Sec John Skerritt. I apologise for the delay in sending this through.
Please provide an update on the Action Items when you are able to.

Education and Social Media report – March 2023 D23-5119059

s22 [redacted], s22 [redacted] and s22 [redacted] joined the meeting and presented the 4. Education and Social Media report for March 2023 noting:

- The Social Media Schedule needs to be updated to cover psychedelics and also the announcement of Pholcodine.
- The media release for Pholcodine will go out at 2pm tomorrow.
- Team to update the wording in the social media posts from the talking points for the Minister.
- Need to do Social media on Pholcodine (after 2pm tomorrow) including paid social media (about $10k) for both psychedelics and Pholcodine.
- Of the items on the forward plan –exclude microneedling and one other to make space for Psychedelics and Pholcodine.
- For Psychedelics – target both consumers and Health Care Professionals with messaging finessed as appropriate.
- Messaging for industry will also be required along with more guidance on psychedelics.
- There is a webinar on Wednesday.
- Another round of social media on Pholcodine will be needed at end of March when the decision takes effect.

The HPRG Executive also discussed:

- Examples of the latest template for social media posts were shared on the screen. The new template for Industry updates, and the Health professionals updates are done fortnightly or weekly.
- It would be helpful to get some statistics on the views from the new templates. There will be some reporting done, but there are some limitations in the reporting capabilities of the platform.

The HPRG Executive considered the recommendations and:

1. **NOTED** the status of work currently in progress across education priority areas

1. **NOTED** the January 2023 social media highlights

2. **APPROVED WITH UPDATES** the March 2023 Social Media Schedule at Attachment A D23-5056602

3. **NOTED** the Safe use and storage of paracetamol campaign performance report at Attachment B D23-5057851

4. **NOTED** the Emerging issues campaign performance report at Attachment C D23-5030597

ACTION ITEM

s22 to update the Social Media schedule to include posts on psychedelics and on Pholcodine.

Let me know if you need anything else.

Regards

s22
s22 to Deputy Secretary John Skerritt

Health Products Regulation Group
(comprising the Therapeutic Goods Administration and the Office of Drug Control)
T: s22 | E: s22 @health.gov.au
Location: Fairbairn Level 2 North - 2.N.461

Australian Government

Department of Health and Aged Care

Ministerial Information Request
MB23-000260
Version (2)
Date sent to MO: 27/02/2023

To: Minister Butler

Subject/Issue: TGA's decision to recall and cancel dry cough lozenges and syrups containing pholcodine

Comments:			
Contact Officer:	*Elspeth Kay*	*Assistant Secretary, Pharmacovigilance Branch, Medicines Regulation Division*	Ph: (02) 6289 3528 M: s22 [redacted]
Clearance Officer:	*Adj Prof John Skerritt*	*Deputy Secretary, Health Products Regulation Group*	Ph: (02) 6289 4200 M: s22 [redacted]

Response:

- A TGA delegate of the Secretary has made the decision to cancel the registration and require a Class II retail level recall of pholcodine containing medicines.
- On 28 February the TGA will send a 'Notice of cancellation under s 30(2)(a) and notice of Requirement to recall action under s 30EA of the of the *Therapeutic Goods Act 1989* (the Act) to each of the 14 pholcodine sponsors. This letter will include a response to their submissions and reasoning for the cancellation and recall:
  - 55 products will be cancelled by the delegate from the Australian Register of Therapeutic Goods (ARTG). Cancellation from the ARTG will take effect on 29 March 2023.
  - 44 products will be recalled from pharmacies at the direction of the TGA delegate (retail level recall, but not a consumer level recall). All recalls must be initiated by 7 March 2023.
  - Nine products will not undergo any recall action as there is no stock available in Australia on pharmacy shelves.
  - Two products have already been recalled from pharmacies on 23 December 2022 and 23 January 2023 with the products' commercial sponsors initiating the recall. There should be no stock remaining in pharmacies for these two products.
- The TGA decision was made in response to the international 'ALPHO' study that found that people have a 420% higher risk of an anaphylactic reaction to a neuromuscular blocking agent in the 12 months after using pholcodine. Similar results indicating a very significant increase in anaphylaxis have also been found in Australian research.

- Anaphylactic reactions are serious and potentially life-threatening and rapid-onset allergic reactions, involving a sudden drop in blood pressure, swelling of the tongue and throat and collapse. It is considered a medical emergency. Neuromuscular blocking agents are often used during general anaesthesia in surgical procedures.
- The TGA's assessment of the evidence is that the safety of pholcodine-containing medicines is unacceptable because it is not possible to identify effective measures to reduce the risk of this potential interaction. Under section 30(2)(a) of the *Therapeutic Goods Act 1989* a delegate of the Secretary may cancel the registration of a medicine if it appears that the quality, safety or efficacy of the goods is unacceptable.
- The TGA sent notices proposing cancellation and recall to all Australian sponsors of pholcodine-containing products in December 2022, giving them a reasonable opportunity to make submissions in relation to the proposed cancellation as required under section 30(3) of the Act. Responses were submitted by all sponsors, the Pharmacy Guild and Consumer Health Products Australia.
- When proposing to cancel specific products on safety grounds, the interaction is directly between the TGA and individual commercial sponsors of those products. The process does not involve public consultation because if a final decision is made not to proceed with cancellation or recall, this could cause commercial damage to the sponsor of the product. In cases where the TGA has concerns regarding the safety of a particular therapeutic good, a lengthy public consultation is particularly unlikely to be appropriate given the possibility that the TGA may need to take urgent action to protect the health of the public.
- The TGA will publish a media release and safety alert on Tuesday 28 February 2023 shortly after communicating the decision to sponsors. Both of these documents are attached for your information.

Background:

<u>Medicines for dry cough</u>

- Pholcodine is an opioid medicine that is used in adults and children to treat non-productive (dry) cough and, in combination with other active substances, is used to treat the symptoms of cold and flu. In Australia this medicine is available in multiple over-the-counter cough and cold medicines.
- There were 55 pholcodine-containing products with 14 sponsors on the ARTG in December 2022. Of these, nine products were not being marketed in Australia.
- Other products are available over the counter for the treatment of dry cough in Australia include dihydrocodeine and dextromethorphan. Sponsors of pholcodine-containing products have advised that pholcodine covers approximately 85% of the market for medicines for dry cough. According to data held by the Department, approximately 1.44 million pholcodine products were sold in Australia between July 2021 and June 2022.
- Acute cough usually resolves without treatment. Over the counter medications available for acute cough, although they are widely used, are not generally clinically recommended because they have limited benefit in acute cough and can cause adverse effects.

- Regulatory pathways are available for the import of foreign English language-labelled alternatives for dry cough, such as syrups and lozenges containing dextromethorphan, to facilitate supply particularly over the winter cold and flu season. Sponsors are familiar with these pathways, and TGA will expedite assessment of applications.

International regulatory status of pholcodine

- Pholcodine-containing medicines are no longer approved in most OECD countries.
- Pholcodine is not prescribed in the United States where it is classed as a Schedule 1 drug (drugs with no currently accepted medical use and a high potential for abuse).
- Apart from Australia, pholcodine-containing products are currently available in the United Kingdom, Singapore, New Zealand (as a pharmacist only medicine) and in a small number of European Union countries (Belgium, Croatia, France, Ireland, Lithuania, Luxembourg and Slovenia)
- In late 2022, the European Medicines Agency's Pharmacovigilance and Risk Assessment Committee (PRAC) recommended the withdrawal of medicines containing pholcodine from the European market in response to the ALPHO study.
- The TGA is aware that all regulators in current markets are reviewing this issue in light of the ALPHO study findings.

The ALPHO study and the risk of anaphylactic reaction

- The ALPHO study is the 'Anaphylaxis to Neuromuscular Blocking Agents (NMBA) and Pholcodine Exposure – Case control study', which was conducted at the request of the European Medicines Agency to investigate whether pholcodine exposure elevated the risk of perioperative anaphylaxis to neuromuscular blocking agents.
- The ALPHO study found that use of pholcodine during the 12 months preceding anaesthesia is linked to a risk of perianaesthetic anaphylactic reaction related to neuromuscular blockers.
- The TGA considers the results of the ALPHO study to be applicable to the Australian context, especially because it is supported by the results of a study conducted in Western Australia between 2012 and 2020, which found that pholcodine consumption was a risk factor for anaphylaxis to neuromuscular blockers.
- Anaphylactic reactions are serious and potentially life-threatening allergic reactions. It is not currently possible to identify a patient population for whom the benefits of pholcodine outweigh the risks in relation to perianaesthetic anaphylactic reaction because:
    - no pathology testing is considered accurate
    - patients may not remember what medicines they have taken
    - there may be times when the patient is unconscious and cannot give a medication history prior to surgery
    - anaesthetists may not ask patients about their previous use of over-the-counter medicines.
- The Australian and New Zealand College of Anaesthetists (ANZCA) have previously raised this safety issue with the TGA and have indicated they are aware of the ALPHO study findings. It is expected that ANZCA would be supportive of regulatory action implemented by the TGA regarding cancellation and recall of pholcodine products.

Cancellation and recall of pholcodine-containing medicine from the ARTG

- Cancellation and recall of a medicine from the ARTG on the grounds of unacceptable quality, safety or efficacy is an administrative decision taken by a delegate of the Secretary under the Act.
- On 20 December 2022, the TGA sent a 'Notice of proposal to cancel registration under s 30(2)(a) and notice of proposal to require recall action under s 30EA of the of the Act in relation to pholcodine' (Proposal to Cancel and Recall) for 41 products (14 sponsors).
- On 9 January 2023, the TGA sent a second Proposal to Cancel and Recall for 14 further identified pholcodine-containing products (3 sponsors).
- The TGA provided two extensions for sponsors to provide responses. The final date for all responses to be provided was 20 January 2023.
- All 14 sponsors, along with The Pharmacy Guild and Consumer Healthcare Products Australia (CHPA) provided a response to the notice of proposal to cancel and recall.
- On 10 February 2023, following legal advice, the TGA released additional information to sponsors including redacted Australian adverse event reports relating to pholcodine sensitisation and the Pharmacy Guild and CHPA responses. Submissions raised by other sponsors were also released to ensure procedural fairness to all sponsors. The TGA requested that sponsor submissions to these additional documents be provided by 20 February 2023.
- Four sponsors provided submissions responding to these additional documents.
- The cancellation of pholcodine-containing medicines from the ARTG will take effect on 29 March 2023. This will provide the sponsors with 21 working days from receipt of the notice to cease the advertising, importation, manufacture, export and supply of the goods before the cancellation takes effect.
- Sponsors are required to commence recall action no later than 7 March 2023. Sponsors will have a maximum of five working days from the date the Notice is sent to initiate the required Class II recall.
- Prompt action to remove a product from the market is considered appropriate in cases where a safety issue has been identified.
- The decision made by the delegate is reviewable under s60 of the Act, wherein reconsideration of the initial decision can be sought, although a request for such a review does not place a stay on implementation the initial decision during the review.

Current recall actions in relation to pholcodine safety concerns

- Some companies have already decided to recall products ahead of any decision being made by the TGA. As of 22 February 2023, two class II, retail level recalls have been undertaken by Generic Health Pty Ltd and Sanofi Consumer Healthcare (RC-2022-RN-01564-1 & RC-2023-RN-00071-1). Both sponsors voluntarily notified the TGA of their intention to initiate the recall of their products from the market prior to any decisions on regulatory action being made by the TGA due to current safety concerns.
- As part of these recalls, wholesalers and pharmacies were advised to inspect their stock and immediately cease further distribution. Pharmacies were advised to return impacted stock to their wholesalers to receive a credit.

Attachments

A. Talking points

B. Pholcodine safety alert for TGA website

C. Media release: Pholcodine cough medicines cancelled by the TGA and recalled from pharmacies for safety reasons

Attachment A: Talking points

- The TGA has decided to cancel and recall pholcodine-containing medicines from the Australian Register of Therapeutic Goods. This decision means that pholcodine-containing syrups, oral solutions and lozenges are being withdrawn from Australian pharmacy shelves.
- The TGA made this decision following an investigation of new safety data arising from Europe which showed a link between pholcodine and a risk of serious allergic reactions to muscle relaxant medicines used during general anaesthesia (called neuromuscular blocking agents).
- The TGA's investigation followed a review by the European Medicines Agency (EMA) recommending the withdrawal of pholcodine-containing products in Europe.
- Pholcodine has been used to treat dry cough and in combination with other medicines in cold and flu products. Pholcodine is available over the pharmacy counter under various trade names and generic brands.
- Although the overall risk of anaphylaxis during anaesthesia is low, the increased risk was significant and withdrawing pholcodine from the Australian market was the only regulatory option that could mitigate this safety concern.
- On the basis of this new safety information, health professionals should advise consumers to stop taking pholcodine-containing medicines and consider appropriate alternatives to treat their dry cough symptoms.
- Health professionals should also check whether patients scheduled to undergo general anaesthesia have used pholcodine and should remain aware of the risk of anaphylactic reactions in these patients.
- I also urge consumers to check if any over-the-counter cold and flu medicines in the cupboard contain pholcodine and, if they do, ask your doctor or pharmacist to suggest an alternative treatment.
- The TGA will issue advice to health professionals and consumers once notices have been sent to sponsors and will work closely with health professional groups to ensure awareness of this safety issue.

Minister	**Minister Butler**
PDR Number	**MB23-000260**
Subject	****Urgent one day turnaround** MIR - Briefing on TGA's proposal to recall and cancel dry cough lozenges and syrups containing pholcodine**
Contact Officer	Elspeth Kay (02) 6289 3528 s22 [redacted]
Clearance Officer	Adj Prof John Skerritt (02) 6289 4200 s22 [redacted]
Division/Branch	|Health Products Regulation| Medicines Regulation

Adviser/DLO comments:	Returned to Dept for: REDRAFT ☐ NFA ☐

Pholcodine

TGA cancels the registration of all pholcodine medicines from Australian market

Related information

- About recall actions
- EMA recommends withdrawal of pholcodine medicines from EU market | European Medicines Agency (europa.eu)

28 February 2023

Following an investigation into the safety of pholcodine-containing medicines, the Therapeutic Goods Administration (TGA) has decided to cancel the registration of all such medicines in Australia and is recalling them from pharmacy shelves.

Pholcodine has been used in adults and children to treat non-productive (dry) cough and is most commonly used in cough syrups and lozenge products. It has also been used in combination with other active substances in products that treat the symptoms of cold and flu.

The TGA investigation follows a review by the European Medicines Agency (EMA) recommending the withdrawal of marketing authorisations for these products.

The EMA review supports a previously suspected link between pholcodine-containing medicines and a risk of anaphylactic reactions (a sudden, severe and life-threatening allergic reaction) to medicines called neuromuscular blocking agents (NMBAs) which are used as muscle relaxants during general anaesthesia.

What the EMA review evaluated

The EMA review was carried out by the Pharmacovigilance Risk Assessment Committee. During the review, the Committee evaluated all available evidence including the final results of the ALPHO study, post-marketing safety data and information submitted by third parties such as health professionals. The data showed that use of pholcodine in the 12 months before general anaesthesia with NMBAs puts people at risk of developing an anaphylactic reaction to these agents.

What is the TGA doing?

After investigating this safety issue, the TGA has decided to cancel the registration of all pholcodine-containing medicines in Australia and is recalling any pholcodine-containing medicines from pharmacy shelves.

We consider that the recommendations by the EMA and the results of the ALPHO study are applicable to the Australian population. This is supported by a Western Australian study which showed that previous pholcodine consumption was a statistically significant risk factor for NMBA anaphylaxis.[1]

A search of the TGA's Database of Adverse Event Notifications (DAEN) on 9 February 2023 identified 51 Australian cases of suspected pholcodine-related anaphylactic reactions to NMBAs. This included one fatality. These reports of NMBA anaphylaxis documented either previous pholcodine use or test results indicating increased hypersensitivity to pholcodine. Sixteen of these cases have been published in the medical literature.[2-6]

Anaphylactic reactions are serious and potentially life-threatening. However, while patients undergoing surgery are typically asked about the prescription medicines they may currently being treated with in preparation for the procedure, hospitals and surgery facilities do not consistently ask about over the counter medicine use such as cough lozenges and syrups, especially if such use was some months earlier.

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, the TGA is cancelling the registration of all pholcodine-containing medicines in Australia and is recalling products from pharmacies.

What should consumers do?

Check if any of your over-the-counter cold and flu medicines contain pholcodine. Pholcodine is particularly used in cough lozenge or syrup products, but can be found in other medicines. If they do, ask your doctor or pharmacist to suggest an alternative treatment.

If you need general anaesthesia and have taken pholcodine in the past 12 months, tell your health professional prior to the procedure. It may help to show this safety alert to your doctor.

What should health professionals do?

Health professionals should advise patients to stop taking pholcodine-containing medicines and consider appropriate alternatives to treat their symptoms.

Health professionals should also check whether patients scheduled to undergo general anaesthesia with NMBAs have used pholcodine in the previous 12 months and should remain aware of the risk of anaphylactic reactions in these patients.

More about pholcodine

Pholcodine is an opioid medicine that works directly in the brain, suppressing the cough reflex by reducing the nerve signals that are sent to the muscles involved in coughing.

Pholcodine has been used as a cough suppressant since the 1950s and has been available over-the-counter from pharmacies. Cold and flu medicines often contained pholcodine in combination with other substances and were available as oral liquids and lozenges under various trade names and as generics.

Further reading

1. Sadleir PHM, et al. Relationship of perioperative anaphylaxis to neuromuscular blocking agents, obesity, and pholcodine consumption: a case-control study. Br J Anaesth. 2021 126(5):940-948. doi: 10.1016/j.bja.2020.12.018.
2. Li J, et al. Integrating basophil activation tests into evaluation of perioperative anaphylaxis to neuromuscular blocking agents. Br J Anaesth. 2019 123(1):135-143. doi: 10.1016/j.bja.2019.02.024.
3. Pedersen AF, et al. Failure to investigate anaesthetic anaphylaxis resulting in a preventable second anaphylactic reaction. Anaesth Intensive Care. 2012 Nov;40(6):1053-5. doi: 10.1177/0310057X1204000619.
4. Gurunathan U, et al. Coronary vasospasm in the setting of perioperative anaphylaxis: A case report. Anaesth Intensive Care. 2022 50(6):491-494. doi: 10.1177/0310057X221088602.
5. Brusch AM, et al. Exploring the link between pholcodine exposure and neuromuscular blocking agent anaphylaxis. Br J Clin Pharmacol. 2014 78(1):14-23. doi: 10.1111/bcp.12290.
6. Lee J, et al. Pholcodine-associated allergy and cross-reactivity with neuromuscular blocking drugs. Intern Med J. 2016 46(S4):17. doi: 10.1111/imj.40_13197.

Reporting problems

Consumers and health professionals are encouraged to report problems with medicines or vaccines. Your report will contribute to the TGA's monitoring of these products.

The TGA cannot give advice about an individual's medical condition. You are strongly encouraged to talk with a health professional if you are concerned about a possible adverse event associated with a medicine or vaccine.

- Category: Alert/Advisory, Medicines safety
- Tags: pholcodine, cough suppressants, perianaesthetic anaphylactic reaction

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

MEDIA RELEASE

Pholcodine cough medicines cancelled by the TGA and recalled from pharmacies for safety reasons

28 February 2023

Following a safety investigation by the Therapeutic Goods Administration (TGA), 55 products containing pholcodine are being cancelled from the Australian Register of Therapeutic Goods and those currently on pharmacy shelves are being recalled from pharmacies.

The cancellation and recall actions are being taken because of a link between pholcodine-containing medicines and an increased risk of anaphylactic reactions (a sudden, severe and life-threatening allergic reaction) to certain medicines used as muscle relaxants during general anaesthesia (called neuromuscular blocking agents).

Pholcodine has been used in a wide range of over the counter pharmacy medicines to treat non-productive (dry) cough, particularly in syrups and lozenges. It is also used in combination with other medicines in products that treat the symptoms of cold and flu.

TGA Head Adjunct Professor John Skerritt said: “It is difficult to reliably predict who may be at risk of anaphylaxis during anaesthesia and some patients may not know if they have taken pholcodine medicines recently.

“Some patients undergoing emergency surgery may not be in a position to talk to their anaesthetist at all. In addition, while surgical facilities may ask about which prescription medicines a patient is taking, they may not ask about over the counter products”

“Fortunately, safer alternatives to treat a dry cough are available and consumers should ask their doctor or pharmacist for advice. I urge consumers to check if any of your over-the-counter cold and flu medicines contain pholcodine and, if they do, ask your doctor or pharmacist to suggest an alternative treatment”.

“If you will need general anaesthesia and have taken pholcodine in the past 12 months, I advise you to tell your health professional. “Health professionals should also check whether

patients scheduled to undergo general anaesthesia have used pholcodine in the previous 12 months."

The TGA's investigation followed a review by the European Medicines Agency (EMA) recommending the withdrawal of marketing authorisations for these products in Europe. The European findings were supported by a Western Australian study which also showed that pholcodine was a risk factor. Up to February 9 this year, the TGA has also received 51 reports of Australian cases of suspected pholcodine-related anaphylactic reactions to neuromuscular blockers, including one fatality.

Contact for members of the media:

- Email: news@health.gov.au
- Phone: 02 6289 7400

Australian Government

Department of Health and Aged Care

Choose an item.

MB23-000260

Version (1)

Date sent to MO: Click or tap to enter a date.

To: Minister Butler

Subject/Issue: **Urgent one day turnaround MIR - Briefing on the TGA's proposal to recall and cancel medicines containing pholcodine**

Comments:			
Contact Officer:	*Elspeth Kay*	*Assistant Secretary, Pharmacovigilance Branch, Medicines Regulation Division*	Ph: (02) 6289 3528 M: s22 [redacted]
Clearance Officer:	*Adj Prof John Skerritt*	*Deputy Secretary, Health Products Regulation Group*	Ph: (02) 6289 4200 M: s22 [redacted]

Response:

- The TGA is currently considering responses from industry sponsors to a proposal to cancel and require recall of all pholcodine-containing products on the Australian Register of Therapeutic Goods (ARTG) in response to an international 'ALPHO' study that found that people have a 420% higher risk of an anaphylactic reaction to a neuromuscular blocking agent in the 12 months after using pholcodine.
- Anaphylactic reactions are serious and potentially life-threatening allergic reactions, involving a sudden drop in blood pressure, swelling of the tongue and throat and collapse. It is considered as a medical emergency. Neuromuscular blocking agents are often used during general anaesthesia in surgical procedures.
- The TGA's assessment of the evidence is that the safety of pholcodine-containing goods is unacceptable because it is not possible to identify effective measures to reduce the risk of this potential interaction. Under section 30(2)(a) of the *Therapeutic Goods Act 1989* a delegate of the Secretary may cancel the registration of a medicine if it appears that the quality, safety or efficacy of the goods is unacceptable.
- The TGA sent notices proposing cancellation and recall to all Australian sponsors of pholcodine-containing products in December 2022, giving them a reasonable opportunity to make submissions in relation to the proposed cancellation as required under section 30(3) of the Act. Responses were submitted by all sponsors, the Pharmacy Guild and Consumer Health Products Australia.

- No decision has been made by the TGA on the cancellations and recalls, but a final decision is expected within two weeks. The decision maker will consider relevant scientific and other evidence and the submissions made by sponsors of the affected medicines and industry bodies.
- When proposing to cancel specific products on safety grounds, the interaction is directly between the TGA and individual commercial sponsors of those products. The process does not involve public consultation as if a final decision is made not to proceed with cancellation or recall, this could cause potential commercial damage to the sponsor of the product. In cases where the TGA has concerns regarding the safety of a particular therapeutic good, a lengthy public consultation is particularly unlikely to be appropriate given the possibility that the TGA may need to take urgent action to protect the health of the public.

Background:

Medicines for dry cough

- Pholcodine is an opioid medicine that is used in adults and children to treat non-productive (dry) cough and, in combination with other active substances, is used to treat the symptoms of cold and flu. In Australia this medicine is available in multiple over-the-counter cough and cold medicines.
- There were 55 pholcodine-containing products with 14 sponsors on the Australian Register of Therapeutic Goods in December 2022. Of these, eight products were not being marketed in Australia.
- Other products are available over the counter for the treatment of dry cough in Australia include dihydrocodeine and dextromethorphan. Sponsors of pholcodine-containing products have advised that pholcodine covers approximately 85% of the market for medicines for dry cough. According to data held by the Department, approximately 1.44 million pholcodine products were sold in Australia between July 2021 and June 2022.
- Acute cough usually resolves without treatment. Over the counter medications available for acute cough, although they are widely used, are not generally clinically recommended because they have limited benefit in acute cough and can cause adverse effects.
- If a decision is made to cancel pholcodine-containing products, the TGA will investigate options to expedite the import of foreign English language-labelled alternatives for dry cough, such as syrups and lozenges containing dextromethorphan, to facilitate supply particularly over the winter cold and flu season.

International regulatory status of pholcodine

- Pholcodine-containing medicines are no longer approved in most OECD countries.
- Pholcodine is not prescribed in the United States where it is classed as a Schedule 1 drug (drugs with no currently accepted medical use and a high potential for abuse).
- Apart from Australia, pholcodine-containing products are currently available in the United Kingdom, Singapore, New Zealand (as a pharmacist only medicine) and in a small number of European Union countries (Belgium, Croatia, France, Ireland, Lithuania, Luxembourg and Slovenia)

- In late 2022, the European Medicines Agency's Pharmacovigilance and Risk Assessment Committee (PRAC) has recommended the withdrawal of medicines containing pholcodine from the European market in response to the ALPHO study.
- The TGA is aware that all regulators in current markets are reviewing this issue in light of the ALPHO study findings.

The ALPHO study and the risk of anaphylactic reaction

- The ALPHO study is the 'Anaphylaxis to Neuromuscular Blocking Agents (NMBA) and Pholcodine Exposure – Case control study', which was conducted at the request of the European Medicines Agency to investigate whether pholcodine exposure elevated the risk of perioperative anaphylaxis to neuromuscular blocking agents.
- The ALPHO study found that use of pholcodine during the 12 months preceding anaesthesia is linked to a risk of perianaesthetic anaphylactic reaction related to neuromuscular blockers.
- The TGA considers the results of the ALPHO study to be applicable to the Australian context.
- Anaphylactic reactions are serious and potentially life-threatening allergic reactions. It is not currently possible to identify a patient population for whom the benefits of pholcodine outweigh the risks in relation to perianaesthetic anaphylactic reaction because:
    - No pathology testing is considered accurate
    - patients may not remember what medicines they have taken
    - there may be times when the patient is unconscious and cannot give a medication history prior to surgery
    - anaesthetists may not ask patients about their previous use of over-the-counter medicines.
- The Australian and New Zealand College of Anaesthetists (ANZCA) have previously raised this safety issue with the TGA and have indicated they are aware of the ALPHO study findings. It is expected that ANZCA would be supportive of regulatory action in the event that pholcodine products were cancelled from the ARTG.

Process for proposing to cancel a medicine from the ARTG

- Cancellation of a medicine from the ARTG on the ground of unacceptable quality, safety or efficacy is an administrative decision taken by a delegate of the Secretary under the *Therapeutic Goods Act 1989.*
- If the delegate decides to require cancellation and recall of pholcodine-containing products, it is likely that sponsors will be given a week to recall their products and 20 working days before the cancellation takes effect. Prompt action to remove a product from the market is considered appropriate in cases where a safety issue has been identified.
- Any decision made by the delegate is reviewable under s60 of the Therapeutic Goods Act, wherein reconsideration of the initial decision can be sought, although a request for such a review does not place a stay on implementation the initial decision during the review.

- On 20 December 2022, the TGA sent a 'Notice of proposal to cancel registration under s 30(2)(a) and notice of proposal to require recall action under s 30EA of the of the Therapeutic Goods Act 1989 in relation to pholcodine' for 41 products (14 sponsors).
- The TGA provided two extensions for sponsors to provide responses. The final date for all responses to be provided was 20 January 2023.
- All 14 sponsors, along with The Pharmacy Guild and Consumer Healthcare Products Australia (CHPA) provided a response to the notice of proposal to cancel and recall.

Recall actions in relation to pholcodine safety concerns

- Some companies have already decided to recall products ahead of any decision being made by the TGA> As of 24 January 2023, two class II, retail level recalls have been undertaken by Generic Health Pty Ltd and Sanofi Consumer Healthcare (RC-2022-RN-01564-1 & RC-2023-RN-00071-1). Both sponsors voluntarily notified the TGA of their intention to initiate the recall of their products from the market prior to any decisions on regulatory action being made by the TGA due to current safety concerns.
- As part of these recalls, wholesalers and pharmacies were advised to inspect their stock and immediately cease further distribution. Pharmacies were advised to return impacted stock to their wholesalers to receive a credit.

Minister	**Minister Butler**
PDR Number	**MB23-000260**
Subject	****Urgent one day turnaround** MIR - Briefing on TGA's proposal to recall and cancel medicines containing pholcodine**
Contact Officer	Elspeth Kay (02) 6289 3528 s22 [redacted]
Clearance Officer	Adj Prof John Skerritt (02) 6289 4200 s22 [redacted]
Division/Branch	|Health Products Regulation| Medicines Regulation

Adviser/DLO comments:	Returned to Dept for: REDRAFT ☐ NFA ☐