31 March 2023

South African Society of Anaesthesiologists
PO Box 252511
Glenashley, 4022
SOUTH AFRICA
Email: sasa@sasaweb.com
Website: http://www.sasaweb.com
Phone: +27 86 010 3137

IMPORTANT MEDICINE SAFETY INFORMATION

Dear Doctor,

RE: PHOLCODINE-CONTAINING MEDICINES – POTENTIAL RISK OF PERIANAESTHETIC ANAPHYLACTIC REACTION RELATED TO NEUROMUSCULAR BLOCKING AGENTS (NMBAs) POST PHOLCODINE USE

iNova Pharmaceuticals in agreement with the South African Health Products Regulatory Authority (SAHPRA) wish to inform you of the potential risk of perianaesthetic anaphylactic reaction related to neuromuscular blocking agents (NMBAs) post use of pholcodine-containing medicines.

Summary

- Use of pholcodine within 12 months preceding anaesthesia with neuromuscular blocking agents (NMBAs) has been linked to a risk of perianesthetic anaphylactic reaction to NMBAs.
- No effective measures have been identified to minimise this risk in patients exposed to pholcodine-containing medicinal products.
- As a consequence, pholcodine-containing medicinal products are being withdrawn from the European Union market, United Kingdom, Australian, Malaysian and recently (28 March 2023) the South African market as well. Please refer to the attached Recall letter.
- In case of anaesthesia requiring administration of NMBAs, doctors should check whether patients have used pholcodine-containing medicinal products in the last 12 months and if so, maintain awareness of potential perianaesthetic anaphylactic reactions to NMBAs.

Background on the safety concern

Pholcodine is an opioid medicine that is used for the treatment of non-productive (dry) cough in children and adults. Pholcodine-containing medicinal products have been the subject of two European Union safety reviews in 2011 and in 2022 regarding the potential risk that pholcodine may lead to IgE-sensitisation to neuromuscular blocking agents (NMBAs) and to anaphylactic reactions as a result.

In 2011, the safety review concluded that the benefit-risk balance of pholcodine-containing medicinal products in the treatment of non-productive cough was positive

under normal conditions of use. However, it was concluded that the possibility of an association between pholcodine use and a perianaesthetic anaphylactic reaction to NMBAs should be further investigated. Therefore, a post-authorisation safety study (PASS) was imposed.

In 2022, the final results of the PASS, called ALPHO study, became available showing a link between use of pholcodine within 12 months preceding anaesthesia with NMBAs and a risk of perianesthetic anaphylactic reaction related to NMBAs. Data about the risk related to the use of pholcodine beyond the period of 12 months was not available.

In December 2022, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) assessed the final results of the ALPHO study together with additional data, including data from available medical literature and post-marketing experience. The PRAC could not identify effective measures to minimise the risk for the patients, nor identify a patient population for whom the benefits of pholcodine-containing medicinal products could outweigh its risks. Therefore, marketing of these medicinal products was stopped, and it was recommended that therapeutic alternatives should be selected. Additionally, patients should be advised to stop treatment with pholcodine-containing medicinal products. In case of anaesthesia requiring administration of NMBAs, healthcare professionals were advised to check whether patients have used pholcodine-containing medicinal products in the last 12 months and if so, maintain awareness of potential perianaesthetic anaphylactic reactions to NMBAs.

On 15 March 2023, the Pharmacovigilance Advisory Committee (PVC) of SAHPRA discussed a review regarding the risk of perianaesthetic anaphylactic reaction post pholcodine-containing medicines use. SAHPRA concluded that the reviewed available data from literature and French National Agency provided sufficient evidence to support the association of the risk of perianaesthetic anaphylactic reaction and pholcodine. Additionally, the decisions by other countries' Regulatory Authorities were considered by SAHPRA, including Australia's Therapeutic Goods agency (TGA) and the European Medicines Agency (EMA) to recall and deregister all pholcodine-containing medicines.

On 28 March the outcome of SAHPRAs assessment was communicated to iNova Pharmaceuticals. This included that, based on the available data, there are no possible effective risk minimization measures which have been identified to mitigate against this risk, nor to identify a patient population for whom the benefits of pholcodine outweigh the risks. Furthermore, pholcodine is an over-the-counter cough suppressant therefore there are no prescription records available for prescribers to assess before surgery and patients may not always remember when they have taken a pholcodine-containing medicine.

Due to these considerations and the nature of the adverse reactions (including its unpredictability and clear timelines to onset), SAHPRA too considers the risk of perianaesthetic anaphylactic reaction to outweigh the benefits (cough suppressant effect) of pholcodine-containing medicine and has therefore recommended the withdrawal of all pholcodine-containing medicines from the South African market and a class II type B recall.

Actions to be taken by anaesthesiologists

- In case of anaesthesia requiring administration of NMBAs, healthcare professionals should check whether patients have used pholcodine-containing medicinal products in the last 12 months and if so, maintain awareness of potential perianaesthetic anaphylactic reactions to NMBAs.

Products in the iNova portfolio impacted by this significant safety issue under the PHOLTEX brand in South Africa are the following:

Product name	Product registration no.	Marketing status
Pholtex Junior	29/10.1/0013	Marketed
Pholtex Forte	32/10.1/0116	Marketed
Pholtex Plus	46/16.5/0711	Marketed

Call for adverse event reporting

Doctors are requested to report any spontaneous suspected adverse reactions to iNova Pharmaceuticals (Pty) Ltd at:

- Email: vigilance.zaf@inovapharma.com
- Telephone: +27 11 087 0000.
- Website: www.inovapharma.co.za

Should you have any queries, please do not hesitate to contact me.

Kind regards,

Name	Title	Designation	Contact details
Praenisha Ramnath	Mrs.	Pharmacovigilance Manager	Tel: +27 11 087 0000 e-mail: p.ramnath@inovapharma.com