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ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

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- All pholcodine-containing medicines have been withdrawn in Singapore with effect from 22 June 2023. The product registrant had cancelled the registrations for all pholcodine-containing products in Singapore and ceased their supply to pharmacies, clinics, and healthcare institutions
- This was following HSA's assessment of the available evidence, including the findings from a post-authorisation safety study (ALPHO) which found an increased risk of developing neuromuscular blocking agent (NMBA)-related perioperative anaphylaxis (POA) in patients within 12 months of prior exposure to pholcodine
- Considering these and various factors, HSA concluded that although the absolute risk of pholcodine-associated POA with NMBAs was assessed to be very small, the benefit of pholcodine as a non-productive cough suppressant did not outweigh its associated risk of cross-sensitisation and POA to NMBAs
- Given the relatively long risk period of pholcodine-associated cross-sensitisation i.e. 12 months, patients who had taken the medicine within this time frame may have a small risk of developing POA to NMBAs

Advisory

- Anaesthesiologists and anaesthetists are advised to ask patients who are scheduled to undergo general anaesthesia involving the use of NMBAs whether they have used pholcodine, particularly in the past 12 months, and to maintain clinical vigilance for potential NMBA-related POA in their patients

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- Biotin, also known as vitamin B7, is involved in the metabolism of fats, carbohydrates and amino acids required for protein synthesis. It is commonly present in health supplements
- Biotin may interfere with thyroid function tests, leading to either falsely decreased thyroid stimulating hormone (TSH), or falsely increased triiodothyronine (T3) and thyroxine (T4) levels
- The risk of interference increases with higher doses of biotin

Advisory

- Healthcare professionals are reminded to consider the possibility of biotin interference when interpreting results of thyroid function tests, especially if there is a lack of coherence with the clinical presentation observed

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- Emerging overseas reports of suicidal thoughts and self-harm associated with the use of liraglutide and semaglutide for weight management have triggered safety reviews by overseas regulatory authorities
- HSA's assessment of this potential risk with GLP-1 RA is ongoing, and we are closely monitoring the international developments
- To date, HSA has not received any local adverse event (AE) reports of suicidal thoughts or self-harm associated with GLP-1 RA

Advisory

- Healthcare professionals are advised to exercise caution in the use of these products. Healthcare professionals are also encouraged to report suspected serious AEs related to GLP-1 RA to the Vigilance and Compliance Branch of HSA

Published by the Health Products Regulation Group, HSA and the HSA Product Vigilance Advisory Committee

Reports of issues associated with the use of Cathejell (lignocaine 2% gel)

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- HSA has received feedback from healthcare professionals on issues with the use of Cathejell, in particular, on Cathejell's accordion syringe and break-off tip design. These include difficulties in controlling the amount of gel dispensed and the creation of a suction effect when the syringe is released during administration
- HSA has worked with the product registrant to update and highlight the administration method on the product packaging

Advisory

- Healthcare professionals who encounter issues with Cathejell are encouraged to provide feedback and report any adverse events to HSA

We welcome your feedback on the draft ICH E6 (R3) GCP Guideline!

In Singapore, clinical trials of therapeutic products and Class 2 Cell, Tissue and Gene Therapy Products are conducted in compliance with the Health Products (Clinical Trials) Regulations[1] and Good Clinical Practice (GCP) (i.e., ICH[2] E6 GCP guideline).

The ICH E6 (R3) Expert Working Group has revised the ICH E6 GCP guideline to address the application of GCP principles in the increasingly diverse trial types and data sources employed to support regulatory and healthcare-related decision-making on drugs. The guideline has also been revised to provide flexibility, where appropriate, to facilitate the use of technological innovations in clinical trials.

The ICH E6 (R3) draft guideline[3] has been available for public consultation since 31 May 2023.

We welcome your comments on the draft guideline (if possible) by 30 September 2023, using the template[4] provided by ICH and email to HPRG_feedback@hsa.gov.sg with the subject title: **ICH <E6 (R3)> Feedback.**

You may refer to our HSA website: https://www.hsa.gov.sg/therapeutic-products/international-collaboration/ich for more information.

References

1. *https://sso.agc.gov.sg/SL/HPA2007-S331-2016*
2. *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: https://www.ich.org/*
3. *https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf*
4. *https://admin.ich.org/sites/default/files/inline-files/ICH_PublicConsultationComments_Template_Stakeholders_2020_1209.xlsx*

Dear Healthcare Professional Letters on safety concerns

Scan/click on QR code

How to report suspected AEs to HSA?

For any suspected AEs, please report to us via the following:

HSA_productsafety@hsa.gov.sg

https://www.hsa.gov.sg/adverse-events

For any enquiries or assistance on AE reporting, please call us at 6866 1111

All website references were last accessed on 1 Sep 2023.

Reminder on the risk of pholcodine-associated perioperative anaphylaxis with neuromuscular blocking agents

Key Points

- All pholcodine-containing medicines have been withdrawn in Singapore with effect from 22 June 2023. The product registrant had cancelled the registrations for all pholcodine-containing products in Singapore and ceased their supply to pharmacies, clinics, and healthcare institutions
- This was following HSA's assessment of the available evidence, including findings from a post-authorisation safety study (ALPHO) which found an increased risk of developing neuromuscular blocking agent (NMBA)-related perioperative anaphylaxis (POA) in patients within 12 months of prior exposure to pholcodine
- Considering these and various factors, HSA concluded that although the absolute risk of pholcodine-associated POA with NMBAs was assessed to be very small, the benefit of pholcodine as a non-productive cough suppressant did not outweigh its associated risk of cross-sensitisation and POA to NMBAs
- Given the relatively long risk period of pholcodine-associated cross-sensitisation i.e. 12 months, patients who had taken the medicine within this time frame may have a small risk of developing POA to NMBAs
- Anaesthesiologists and anaesthetists are advised to ask patients who are scheduled to undergo general anaesthesia involving the use of NMBAs, whether they have used pholcodine, particularly in the past 12 months, and to maintain clinical vigilance for potential NMBA-related POA in their patients

With effect from 22 June 2023, all pholcodine-containing medicines have been withdrawn in Singapore. HSA had, in consultation with its Product Vigilance Advisory Committee, concluded that the benefit of pholcodine for the symptomatic relief of non-productive cough did not outweigh the potential increased risk of perioperative anaphylaxis (POA) with neuromuscular blocking agents (NMBAs). The product registrant had cancelled the registrations for all pholcodine-containing products in Singapore and ceased their supply to pharmacies, clinics, and healthcare institutions in June 2023. Since data from a post-authorisation study showed that the use of pholcodine during the 12 months preceding anaesthesia was associated with an increased risk of POA with NMBAs, the risk period is considered relatively long. Therefore, anaesthesiologists and anaesthetists are advised to ask patients who are scheduled to undergo general anaesthesia with NMBAs, whether they have used pholcodine, particularly in the past 12 months, and to maintain clinical vigilance for potential NMBA-related POA in their patients.

Allergy to Neuromuscular Blocking Agents and Pholcodine Exposure (ALPHO) study

The ALPHO study was a post-authorisation safety study imposed by the European Medicines Agency (EMA) on pholcodine-containing products to investigate the possibility of an association between pholcodine use and NMBA-related anaphylaxis. It was a multicentre case-control study comparing pholcodine exposure within a year before anaesthesia between patients with NMBA-related POA (cases) and control patients with uneventful anaesthesia. Each case was matched to two controls by age, sex, type of NMBA, geographic area, and anaesthesia period.[1]

A total of 167 NMBA-related POA cases were matched with 334 control patients. Overall, 47% of cases and 20% of controls reported the use of pholcodine in the year preceding the anaesthesia index ($p<0.001$). The multivariable analysis showed that pholcodine consumption was associated with NMBA-related POA with an adjusted odds ratio of 4.2 (95% confidence interval 2.3-7.0).

Pholcodine is suspected to cross-sensitise individuals to NMBAs by inducing the production of immunoglobulin E (IgE) antibodies, thereby increasing their susceptibility to develop POA to NMBAs.[2] Although the underlying pathogenic mechanisms have yet to be elucidated, the IgE binding epitopes on both pholcodine and NMBAs contain quaternary ammonium. The ALPHO study found the positive predictive value for specific IgE antibodies to pholcodine and quaternary ammonium to be very low (up to only 5.3%), suggesting that only a small proportion of patients (~ 5 out of 100) who have IgE antibodies to pholcodine/quaternary ammonium will develop POA to NMBAs. This precludes the use of these biomarkers to identify pholcodine-exposed patients who are at high risk of developing POA to NMBAs.

International regulatory actions

Several regulatory agencies, including the European Medicines Agency (EMA), Australia Therapeutic Goods Administration (TGA), United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA), Malaysia National Pharmaceutical Regulatory Agency (NPRA) and Hong Kong Department of Health, have announced the withdrawal of pholcodine-containing products in their jurisdictions.[3-7] These actions were taken following their review of the ALPHO study results and other available information.

HSA's benefit-risk assessment and regulatory actions

HSA's assessment took into consideration the findings from the ALPHO study, use of pholcodine in the local context, availability of therapeutic alternatives, expert opinions of local healthcare professionals (i.e., anaesthesiologists, general practitioners and pharmacists) and the regulatory actions taken by the international health regulatory authorities.

POA is a potentially life-threatening systemic hypersensitivity reaction that typically manifests abruptly after induction of anaesthesia, with severe symptoms that require immediate diagnosis and treatment. The local incidence of POA is considered to be rare and ranges from 1 to 4 in 10,000, with NMBAs identified as the causative agent for up to half of these cases.[8,9] The clinical presentation of POA can vary across patients depending on the triggering agent, underlying comorbidities and concomitant use of other drugs. Hence, the outcome of any NMBA-related POA is dependent on the timeliness and effectiveness of the recognition and management of the anaphylaxis.

The overall absolute risk of pholcodine-associated POA with NMBAs was assessed to be very small given the rare NMBA-specific incidence of POA reported locally and that the risk applies to a small subset of patients with prior exposure to pholcodine who are subjected to an NMBA during the perioperative period. However, there are no effective risk mitigation measures that can reduce the risk of pholcodine-associated POA with NMBAs in

individual patients. There are no biomarkers or tests that can predict which pholcodine-exposed patients will develop POA to NMBAs, and it may not be possible to accurately obtain history of pholcodine use due to poor patient recollection or in situations of emergency surgeries. There is also uncertainty of a longer risk period beyond 12 months.

To date, HSA has not received any local reports of POA to NMBAs associated with prior pholcodine use, although the possibility of under reporting of cases cannot be ruled out.

Considering the serious and life-threatening nature of POA, the clinical necessity of using NMBAs during anaesthesia, the non-serious and self-limiting nature of non-productive coughs, as well as the availability of therapeutic alternatives (e.g., codeine and dextromethorphan), HSA concluded that the benefit of pholcodine did not outweigh its associated risk of cross-sensitisation and POA to NMBAs. The product registrant had cancelled the registrations for all pholcodine-containing products in Singapore and ceased their supply to pharmacies, clinics, and healthcare institutions since June 2023.

HSA's advisory

Given the relatively long risk period of pholcodine-associated cross-sensitisation i.e. 12 months, patients who had taken the medicine within this time frame may have a small risk of developing POA to NMBAs. Anaesthesiologists and anaesthetists are advised to ask patients who are scheduled to undergo general anaesthesia involving the use of NMBAs, whether they have used pholcodine, particularly in the past 12 months, and to maintain clinical vigilance for potential NMBA-related POA in their patients.

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1. *Br J Anaesth. 2023;S0007-0912(23)00104-6*
2. *Allergy. 2006;61(1):49-55*
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Biotin interference with thyroid function tests

Key Points

- Biotin, also known as vitamin B7, is involved in the metabolism of fats, carbohydrates and amino acids required for protein synthesis. It is commonly present in health supplements.
- Biotin may interfere with thyroid function tests, leading to either falsely decreased thyroid stimulating hormone (TSH), or falsely increased triiodothyronine (T3) and thyroxine (T4) levels
- The risk of interference increases with higher doses of biotin
- Healthcare professionals are reminded to consider the possibility of biotin interference when interpreting results of thyroid function tests, especially if there is a lack of coherence with the clinical presentation observed

Biotin, also known as vitamin B7, is involved in the metabolism of fats, carbohydrates and amino acids required for protein synthesis. It is commonly present in health supplements (such as multivitamins, prenatal vitamins, and products promoting hair, skin and nail growth) and may interfere with thyroid function tests that are based on a biotin/streptavidin interaction. Depending on the assay design, this may lead to either falsely decreased or falsely increased test results, resulting in potential patient mismanagement or misdiagnosis. The risk of interference increases with higher doses of biotin. Healthcare professionals are reminded to consider the possibility of biotin interference when interpreting results of thyroid immunoassays, especially when the results do not match the clinical presentation.

Mechanism behind biotin interference with thyroid function tests

Thyroid function tests measure the levels of thyroid hormones in the blood including thyroxine (T4) and triiodothyronine (T3), as well as thyroid stimulating hormone (TSH). These tests are critical in diagnosing and monitoring thyroid disorders. Generally, there are two types of thyroid immunoassays used in the measurement of thyroid function. They are the sandwich assay to measure larger molecules such as TSH, and the competitive assay to measure small molecules such as T3 and T4.[1] These immunoassays utilise the interaction between biotin and streptavidin (a glycoprotein) as a detection method due to the specific binding between the two biomolecules. Exogenous biotin (e.g., from multivitamins or supplements for hair, skin and nails) can therefore interfere with both types of immunoassays, resulting in either a falsely decreased or falsely increased test result, depending on the assay design.[1,2] This potential interaction has been reported with oral products containing ≥ 150 mcg biotin per dose unit and parenteral products containing ≥ 60 mcg biotin per dose unit.[3]

In a TSH sandwich assay, excess biotin occupies the streptavidin binding sites and prevents the binding of TSH-antibody sandwich complex, causing falsely low assay results (Figure 1A). Conversely, in competitive immunoassays where the endogenous analyte (i.e., T3 or T4) competes with the labelled analyte (i.e., source of the signal) for biotinylated antibody binding sites, excess biotin levels result in falsely high assay results. This is because biotin prevents the binding of antibody-labelled analyte and antibody-endogenous analyte to the streptavidin-coated solid phase. The unbound antibodies are removed in the wash step, thereby removing any signal that indicates the concentration of endogenous analyte present. Since the serum concentration of the endogenous analyte is

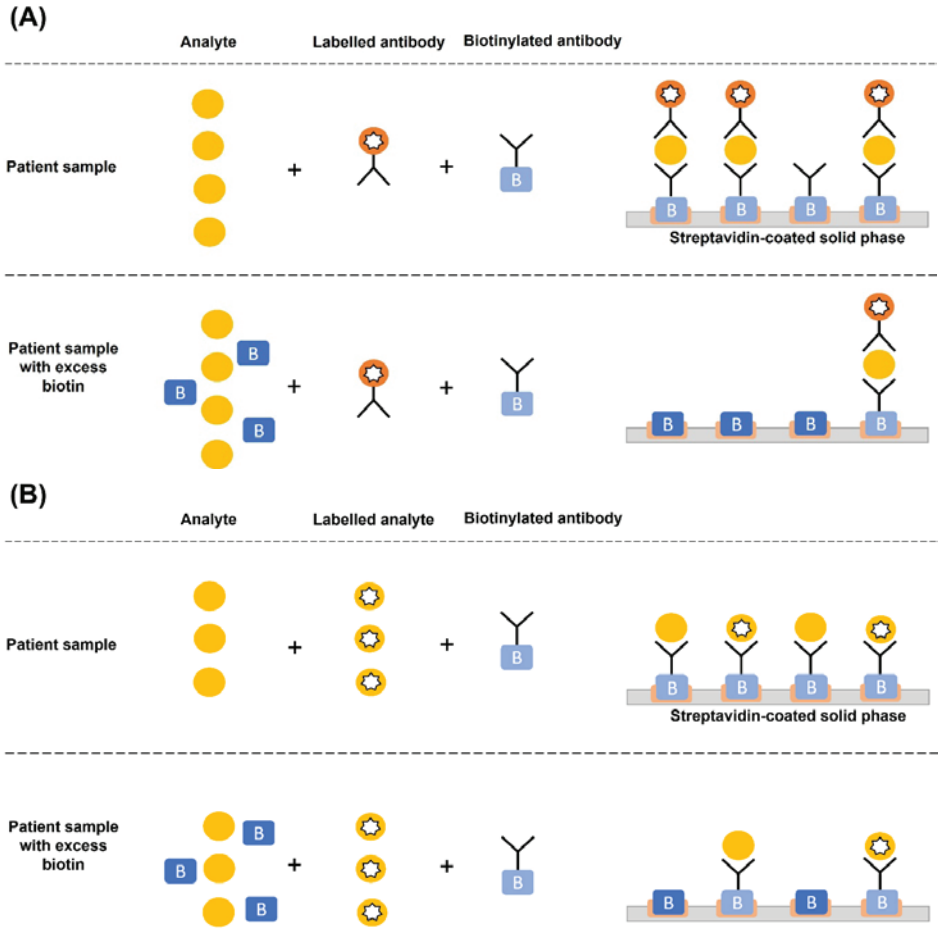

Figure 1. Mechanism of biotin interference in (A) sandwich and (B) competitive immunoassays

inversely proportional to the signal intensity, this results in falsely elevated values (Figure 1B).[1,4]

The interference of biotin with thyroid immunoassays is a known phenomenon and has been documented in several case reports.[4] This had resulted in misdiagnosis or clinical mismanagement of thyroid disorders due to the dependence on thyroid function test results for the initiation or adjustment of thyroid medications.

International regulatory actions

In November 2022, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recommended for the addition of new warnings relating to biotin interference with thyroid function tests to the product information of levothyroxine-containing products. This followed their review on the possible biotin interference with thyroid function tests, which considered the information from spontaneous reports and literature.[5]

Local situation

In 2019, HSA had assessed the possibility of biotin interference with clinical laboratory tests, including thyroid function tests, and worked with the companies to include warnings on the possible interference in the local package inserts (PIs) of parenteral biotin-containing products. This was communicated to healthcare professionals through an article in the ADR News Bulletin (September 2019) issue.[6]

In view that this safety concern may also affect patients who are on levothyroxine therapy, HSA has worked with the product registrants to include similar warnings on the possibility of biotin interference with thyroid function tests in the local PIs of levothyroxine products.

To date, HSA has not received any local adverse event reports of biotin interference causing incorrect thyroid function test results.

HSA's advisory

Healthcare professionals are reminded to consider the possibility of biotin interference when interpreting results of thyroid function tests, especially if there is a lack of coherence with the clinical presentation observed. This may involve asking their patients about the use of biotin health supplements, such as those marketed for hair, skin and nail growth.

References

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6. *HSA ADR News Bulletin 2019 Sep; 21: 3*

Useful Information

Doctors, dentists and pharmacists can claim continuing education points for reading each issue of the HSA ADR News Bulletin. Doctors can apply for one non-core Continuing Medical Education (CME) point under category 3A, dentists can apply for one Continuing Professional Education (CPE) point under category 3A and pharmacists can apply for one patient-care Continuing Professional Education (CPE) point under category 3A per issue of the bulletin.

HSA is assessing the potential risk of suicidal thoughts and self-harm with glucagon-like peptide-1 receptor agonists (GLP-1 RA)

Key Points

- Emerging overseas reports of suicidal thoughts and self-harm associated with the use of liraglutide and semaglutide for weight management have triggered safety reviews by overseas regulatory authorities
- HSA's assessment of this potential risk with GLP-1 RA is ongoing, and we are closely monitoring the international developments
- To date, HSA has not received any local adverse event (AE) reports of suicidal thoughts or self-harm associated with GLP-1 RA
- Healthcare professionals are advised to exercise caution in the use of these products. Healthcare professionals are also encouraged to report suspected serious AEs related to GLP-1 RA to the Vigilance and Compliance Branch of HSA

A safety review on the potential risk of suicidal thoughts and self-harm with glucagon-like peptide-1 receptor agonists (GLP-1 RA) was recently initiated by some overseas regulatory authorities due to emerging reports associated with the use of liraglutide and semaglutide for weight management. HSA is monitoring the international developments closely and working with the local product registrants to assess this potential safety concern. HSA will provide updates when our safety assessment is completed.

GLP-1 RA bind to the GLP-1 receptor and physiologically regulate appetite and calorie intake, thereby enhancing insulin secretion and slowing gastric emptying. They are indicated either for weight management or Type 2 diabetes mellitus (T2DM).

Ongoing reviews by European Medicine Agency (EMA) and UK Medicines and Healthcare Products Regulatory Agency (UK MHRA)

In July 2023, the EMA initiated its review on the potential risk of suicidal thoughts and self-harm in patients taking Saxenda® (liraglutide), Wegovy® (semaglutide) and Ozempic® (semaglutide), due to reports flagged by the Icelandic medicines agency.[1] Saxenda® and Wegovy® are authorised in the European Union (EU) for weight management, whereas Ozempic® is indicated for T2DM but has been used off-label for weight loss. The analysis of the reports is ongoing, and it has not been confirmed whether these reports are linked to the drugs, the patients' underlying conditions or other factors. As further investigation of this signal was warranted, the EMA subsequently extended its review to include the entire class of GLP-1 RA. The UK MHRA has also initiated its review on GLP-1 RA due to domestic reports received on suicidal and self-injurious behaviour with the use of liraglutide and semaglutide.

Local situation

There are currently eight GLP-1 RA products registered locally in Singapore (Table 1).

Table 1. GLP-1 RA products registered in Singapore

Active ingredient	Brand	Product registrant	Indication
Liraglutide	Saxenda®	Novo Nordisk Pharma (Singapore) Pte Ltd	Adjunct to a reduced-calorie diet and increased physical activity for weight management in obese or overweight patients
Semaglutide	Wegovy®	Novo Nordisk Pharma (Singapore) Pte Ltd	
Dulaglutide	Trulicity®	DKSH Singapore Pte Ltd	Adjunct to diet and exercise to improve glycaemic control in patients with T2DM
Liraglutide	Victoza®	Novo Nordisk Pharma (Singapore) Pte Ltd	
Lixisenatide with insulin glargine	Soliqua®	Sanofi-Aventis Singapore Pte Ltd	
Semaglutide	Rybelsus®	Novo Nordisk Pharma (Singapore) Pte Ltd	
Semaglutide	Ozempic®	Novo Nordisk Pharma (Singapore) Pte Ltd	
Tirzepatide	Mounjaro®	DKSH Singapore Pte Ltd	

To date, HSA has not received any local adverse event (AE) reports of suicidal thoughts or self-harm associated with GLP-1 RA. Nevertheless, HSA is closely monitoring the international developments and working with the local product registrants to assess this safety concern. HSA will provide updates when our safety assessment is completed.

HSA's advisory and call for reporting

Healthcare professionals are advised to exercise caution in the use of GLP-1 RA and report suspected serious AEs related to these products to the Vigilance and Compliance Branch of HSA. The following reporting channels may be used:

- Adverse Drug Reactions/Drug Allergy module of the Critical Medical Information Store (CMIS) available in the Electronic Medical Records (EMR) of public healthcare institutions
- Online reporting at https://www.hsa.gov.sg/adverse-events
- Mobile-friendly E-form - scan/click the QR code

References

1. *https://www.ema.europa.eu/en/news/ema-statement-ongoing-review-glp-1-receptor-agonists*

Reports of issues associated with the use of Cathejell (lignocaine 2% gel)

Key Points

- HSA has received feedback from healthcare professionals on issues with the use of Cathejell, in particular on Cathejell's accordion syringe and break-off tip design. These include difficulties in controlling the amount of gel dispensed and the creation of a suction effect when the syringe is released during administration
- HSA has worked with the product registrant to update and highlight the administration method on the product packaging
- Healthcare professionals who encounter issues with Cathejell are encouraged to provide feedback and report any adverse events to HSA

Lignocaine Gel 2% w/w (Cathejell, Pharmaforte Singapore Pte Ltd) is a local anaesthetic in sterile gel form, and is used as a lubricant for catheters, endoscopes or other medical instruments. When applied to mucous membranes, its local anaesthetic and lubricant effects help to alleviate pain during these interventions. Cathejell is currently the only registered sterile lignocaine product in Singapore available in a syringe formulation. Its accordion syringe design with a break-off tip (Figure 1) differs from the design of a traditional syringe. Since late 2022, Cathejell has become more widely used in the public and private healthcare institutions and clinics locally. Cathejell is also marketed in the European Union (EU) and other countries such as Canada and Australia.

Figure 1. Cathejell's accordion syringe and break-off tip design.

Issues and adverse events with Cathejell

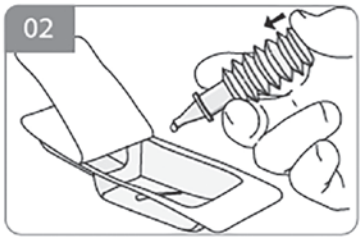
Following the initial feedback received from healthcare professionals in December 2022 which described difficulties with Cathejell when used in procedures such as indwelling catheter (IDC) insertion or cystoscopy, HSA solicited information from other healthcare institutions using Cathejell to better understand the extent of the issue. Not all healthcare institutions experienced similar issues; for those that gave feedback, most of the issues appeared to be related to the accordion syringe design. These include difficulties in controlling the amount of gel dispensed due to the incremental pressure required during administration, making it hard to expel the entire contents of the syringe. This resulted in multiple syringes being used, gel leakage and wastage. Another feedback was that the vacuum created upon the release of the accordion syringe caused a suction effect. This suction effect may cause pain to the patient, or abrasion to the urethral mucosa which can lead to bleeding at the administration site. There was also feedback associated with the length of the tip, as well as the tip being too sharp or having a rough edge.

Three AE cases of administration site bleeding with Cathejell were reported to HSA by two clinicians. In one case, penile tip bleeding occurred following Cathejell administration prior to cystoscope insertion, which the user attributed to an inability to control the amount of gel dispensed due to the syringe design. In the second case, bleeding occurred following Cathejell administration in a patient with benign prostate hyperplasia, and the user attributed it to a product design issue. In the third case, bleeding from the penile urethra occurred when Cathejell was administered for urine catheter insertion.

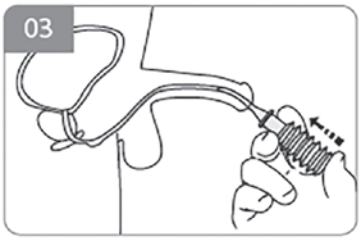
HSA's assessment and follow-up actions

Taking into consideration the three AE cases as well as the information gathered, the cause of the issues could be multifactorial, such as users being unfamiliar with Cathejell's specific administration techniques or Cathejell's inherent product design. Since receiving the feedback, the product registrant has strengthened its efforts in reaching out to end-users to conduct training sessions to reinforce the administration techniques of Cathejell. HSA has worked with the product registrant to update and highlight the administration method on the product's packaging such as the package insert, outer carton (Figure 2) and inner label of individual blisters (Figure 3). HSA has also required the product registrant to strengthen its communication to new users on the administration techniques of Cathejell. These measures aim to increase awareness on the administration techniques and to mitigate potential risks of AEs. HSA will continue to monitor the situation and determine if further measures are necessary. Healthcare professionals who encounter issues with Cathejell are encouraged to provide feedback and report any AEs to HSA. Users may also reach out to the product registrant at pharmacist@pharmaforte.com.sg or +65 64528488 for any queries regarding Cathejell or requests for product training and demonstration.

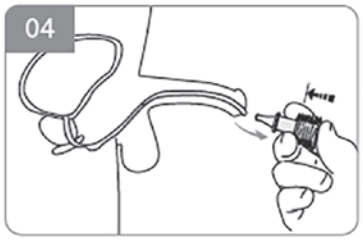
- Clean or disinfect, if appropriate, the external opening of the urethra
- Peel off the paper from the transparent cover-up to the tapered end of the blister (Picture 1)
- Snap off the tip with a short sharp jabbing action into the blister pack (Picture 1)



- Remove the tip completely so that it cannot be inserted accidentally into the urethra
- Squeeze out one drop of gel so that the application nozzle can be inserted more easily (Picture 2)



- Insert the applicator nozzle into the meatus and instill slowly in one gradual and continuous motion. Do not release the syringe during administration. (Picture 3)



- Empty the accordion syringe completely and remove it pressed (Picture 4)
- Wait 5 - 10 minutes before introducing the catheter/instrument.

Figure 2. Cathejell's administration method on the outer carton

Figure 3. Cathejell's administration method on the inner label of individual blisters

Please send your enquiries, comments and suggestions to:

Vigilance and Compliance Branch
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11 Biopolis Way, #11-01,
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Tel : (65) 6866 1111

Website: http://www.hsa.gov.sg
Email : HSA_productsafety@hsa.gov.sg