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# ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

## Health Product Safety Information Summary

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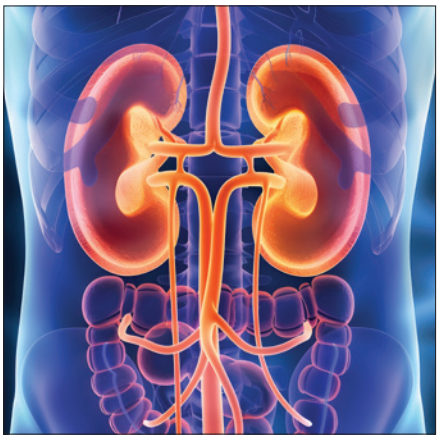
A 69-year-old man with end-stage renal failure requiring haemodialysis was admitted for recurrent arteriovenous graft (AVG) thrombosis. During the admission, he developed anaphylaxis 15 minutes into dialysis. The dialyser membrane was subsequently switched to one that he had previously tolerated at his community dialysis centre, and the remaining dialysis sessions during the admission were completed uneventfully. He was readmitted for recurrent AVG thrombosis a year later and again developed anaphylaxis despite using the same dialyser membrane he had previously tolerated. Elevated serum tryptase levels confirmed true mast cell-mediated anaphylaxis in both episodes. Ethylene oxide was used for sterilisation of the dialysis equipment in one of the episodes, while chlorhexidine topical solution was used as a cleansing agent in both episodes. Heparin was used during both episodes as well as all outpatient haemodialysis sessions. No other medicines were administered during either dialysis session.

***What could have caused the recurrent anaphylaxis in this patient?***

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

## AE Case in Focus 2: Test Yourself Pg 4, 8

A 40-year-old anuric female with end-stage renal disease on long-term peritoneal dialysis presented with a three-day history of progressive confusion, inattentiveness, restlessness, slurred speech, bilateral tremors and truncal ataxia. Examination revealed localised vesicles over the right S1 dermatome and a clean Tenckhoff catheter over the abdomen. She was afebrile, haemodynamically stable, with normal tone, reflexes, power in all limbs, and no signs of meningism. Serum electrolytes, C-reactive protein, procalcitonin, white blood cell count, and computed tomography of the brain were normal.



Five days prior, she had been prescribed oral aciclovir 800 mg five times daily for shingles by a general practitioner. Her other regular medicines were telmisartan, carvedilol, nifedipine, epoetin beta, iron supplement and calcium acetate. She did not take any other supplements or traditional medicine.

***What could have caused the neurological symptoms in this patient?***

## Zoom webinar on Paediatric Gastrointestinal Conditions – Challenges in Primary Care

**6 October 2026, 1.00 – 2.00pm**

### WHY ATTEND?

**PRACTICAL GUIDANCE** on assessment and management of the sick child

**RECOGNISE RED FLAGS** that warrant emergency referral

**LATEST HSA UPDATES** on paediatric GI medications from post-market surveillance

GO gov.sg

https://go.gov.sg/hsa-cfps-webinar

**Topics covered:**

- Clinical management of paediatric gastrointestinal conditions by Dr Christopher Ho, Senior Consultant, Gastroenterology, Hepatology and Nutrition at KK Women's and Children's Hospital
- GI medications in paediatrics: safety signals from post-market surveillance by Ms Aileen Chua, Senior Regulatory Specialist, Vigilance and Compliance Branch, HSA

Joining us in the panel discussion: Dr Sharon Shen, GP, CFPS Council member

This webinar will be submitted for continuing medical education (CME) accreditation

For enquiries, please email us at HSA_productsafety@hsa.gov.sg

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**With support from** KK Women's and Children's Hospital SingHealth · Paeds ENGAGE

**Dear Healthcare Professional Letters on safety concerns**

### 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 AE Adverse Events Watch

**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 September 2026.

# Risk of vitamin B6 deficiency and associated seizures with carbidopa/levodopa or benserazide/levodopa

## Key Points

- Levodopa, in combination with a peripheral decarboxylase inhibitor, such as carbidopa or benserazide, may cause a reduction in vitamin B6 levels, which in turn can lower gamma-aminobutyric acid (GABA) concentrations and increase the risk of seizures.
- Post-market cases of seizures, some with fatal outcomes, have been reported overseas and in published literature in patients using combination therapy of high doses of levodopa (>1,000 mg daily) and a peripheral decarboxylase inhibitor. To date, no cases have been reported locally.
- Healthcare professionals may wish to consider evaluating vitamin B6 levels in patients before and periodically during treatment, or if symptoms suggestive of vitamin B6 deficiency develop. Where a deficiency is identified, vitamin B6 supplementation may be considered where clinically appropriate.

Levodopa, a metabolic precursor to dopamine, is the cornerstone replacement therapy for Parkinson's disease, a neurodegenerative disorder characterised by the loss of dopamine-producing neurons. As levodopa is converted into dopamine via decarboxylation both centrally and peripherally, this limits the amount of levodopa available for delivery across the blood-brain barrier. To enhance its central bioavailability and reduce adverse effects, levodopa is typically co-administered with a peripheral decarboxylase inhibitor, such as carbidopa or benserazide, to prevent the peripheral conversion of levodopa to dopamine.

There are currently 14 products containing levodopa in combination with a peripheral decarboxylase inhibitor registered locally since 1990. Post-market cases of seizures, some with fatal outcomes, have been reported overseas and in published literature in patients using combination products containing levodopa and a peripheral decarboxylase inhibitor. To date, no cases have been reported locally.

## Example of a case report published in the literature

One published overseas case report described a 78-year-old male patient with a six-year history of Parkinson's disease who was taking carbidopa/levodopa and presented with new-onset myoclonus and focal to bilateral tonic-clonic seizures.[1] His Parkinson's disease symptoms had worsened over the preceding five months despite dose escalation of carbidopa/levodopa. Further evaluation showed an undetectable vitamin B6 level (<1 µg/dL), a critically low folate level (<2.2 ng/dL), and video electroencephalography findings consistent with moderate cerebral dysfunction and seizures with diffuse onset. Initially, the seizures did not respond to treatment with two concurrent anti-epileptic drugs (AED). They resolved only after intravenous vitamin B6 replacement together with the addition of the third AED and a five-day course of high-dose steroids. It was concluded that the patient's epileptic events were secondary to depletion of vitamin B6 due to relatively high doses of carbidopa/levodopa.

## Biological plausibility of levodopa and peripheral decarboxylase inhibitor in causing seizures

As vitamin B6 is a cofactor required for the decarboxylation of levodopa to dopamine, the conversion process results in the depletion of vitamin B6 levels.[2,3] In addition, the peripheral decarboxylase inhibitors, carbidopa and benserazide, bind irreversibly to pyridoxal 5'-phosphate (PLP), the active form of vitamin B6, further reducing the availability of functional vitamin B6. PLP is essential for the synthesis of gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system. Reduced vitamin B6 and PLP levels may therefore lead to decreased GABA concentrations and contribute to an increased risk of seizures.

## International regulatory actions

In March 2026, the US Food and Drug Administration (FDA) requested the addition of warnings on the risk of vitamin B6 deficiency and associated seizures to the prescribing information of all products containing carbidopa/levodopa.[4] The US FDA identified 13 post-marketing cases and one case report in published literature, all with features consistent with seizures observed with vitamin B6-dependent epilepsy. These cases involved levodopa doses exceeding 1,000 mg daily, with higher doses (>1,500 mg levodopa) associated with a shorter time from treatment initiation to identification of vitamin B6 deficiency, suggesting a possible dose-related relationship. Nine patients treated with vitamin B6 supplementation had resolution of their seizures, although the majority had previously not responded to multiple AEDs. There were two fatalities, both with documented low vitamin B6 levels and poorly controlled seizures.

## Local situation

HSA has not received any local adverse event reports of vitamin B6 deficiency or associated seizures arising from the use of products containing carbidopa/levodopa or benserazide/levodopa. The package inserts of levodopa-containing products registered locally will be updated to include additional warnings on the risk of reduced vitamin B6 levels and the relevant symptoms, as well as the consequent increased risk of seizures with carbidopa/levodopa or benserazide/levodopa treatment.

## HSA's advisory

Post-marketing reports indicate that seizures associated with vitamin B6 deficiency were refractory to traditional AEDs and resolved after vitamin B6 administration. Healthcare professionals may consider evaluating vitamin B6 levels in patients before initiating and periodically during treatment with carbidopa/levodopa or benserazide/levodopa, and if symptoms suggestive of vitamin B6 deficiency develop. Such symptoms include depression, confusion, cheilosis, glossitis, dermatitis, anaemia, and/or neuropathy. Higher doses of carbidopa/levodopa or benserazide/levodopa may increase the risk of vitamin B6 deficiency and vitamin B6 supplementation may be considered where clinically appropriate.

### References


1. *Case Rep Neurol. 2022; 14: 291–5*
2. *Mov Disord. 2026; 41: 561–4*
3. *Intractable Rare Dis Res. 2014; 3: 52–6*
4. *https://www.fda.gov/drugs/drug-safety-communications/fda-requiring-warning-about-vitamin-b6-deficiency-and-associated-seizures-drug-products-containing*

## AE Case in Focus 1: Test Yourself

A 69-year-old man with end-stage renal failure requiring haemodialysis was admitted for recurrent arteriovenous graft (AVG) thrombosis. During the admission, he developed anaphylaxis 15 minutes into dialysis, manifesting as hypotension, urticaria and angioedema. The dialyser membrane was subsequently switched to one that he had previously tolerated at his community dialysis centre, and the remaining dialysis sessions during the admission were completed uneventfully. About a year later, he was readmitted for recurrent AVG thrombosis and again developed anaphylaxis despite using the same dialyser membrane he had previously tolerated. Serum tryptase[a] levels within two hours of both episodes were raised at 28.6 and 32.5 µg/L, respectively, with significant decline at 24 hours. Ethylene oxide[b] was used for sterilisation of the dialysis equipment in one of the episodes, while chlorhexidine topical solution was used as a cleansing agent in both episodes. Heparin was used during both episodes as well as all outpatient haemodialysis sessions. There were no other medications administered during either dialysis session.

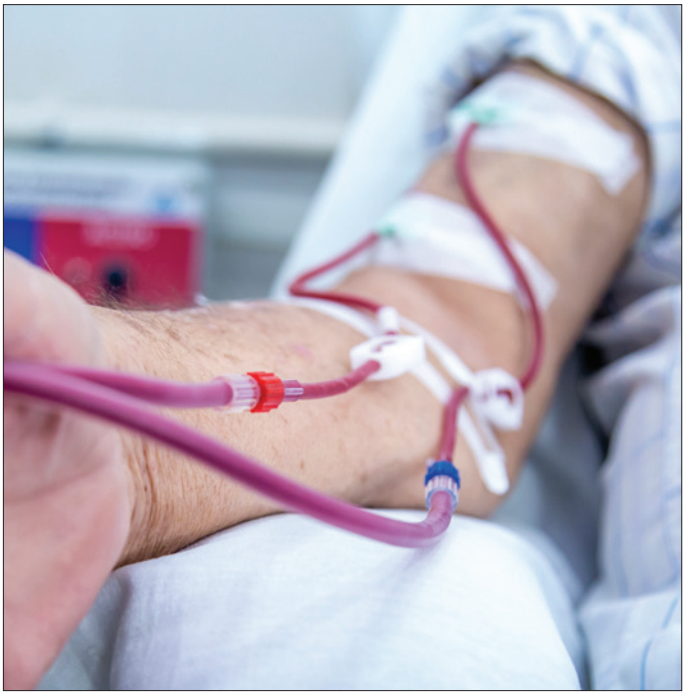
*[a]Tryptase is an enzyme released by mast cells during allergic reactions. It is a biomarker used to confirm anaphylaxis.*

*[b]Ethylene oxide is a chemical sterilising agent commonly used in healthcare settings to sterilise medical devices and equipment that cannot withstand high-temperature steam sterilisation, such as dialysis machines.*

**Question: What could have caused the recurrent anaphylaxis in this patient?**

*HSA would like to thank Dr Chai Zi Teng, Consultant, Department of Dermatology at Singapore General Hospital, for contributing this article.*

Answers can be found on page 7.



## AE Case in Focus 2: Test Yourself

A 40-year-old female with end-stage renal disease secondary to presumptive chronic glomerulonephritis, has been on peritoneal dialysis for the past seven years and was anuric. She presented to the emergency department with gradually worsening confusion over the past three days. Upon review, she was inattentive and restless, with slurred speech, bilateral tremors and truncal ataxia. On examination, the only significant findings were localised vesicles over the right S1 dermatome and a clean Tenckhoff catheter over the abdomen. She was otherwise afebrile, haemodynamically stable, with normal tone, reflexes, power in all limbs, and no signs of meningism. Serum electrolytes, C-reactive protein, procalcitonin, white blood cell count, and computed tomography of the brain were normal.

Her chronic medicines included telmisartan, carvedilol, nifedipine, epoetin beta, iron supplement and calcium acetate. Five days prior to admission, she had seen a general practitioner for shingles and had been prescribed oral aciclovir 800 mg five times a day for one week, which she complied with. She was not taking any other supplements or traditional medicine.

**Question: What could have caused the neurological symptoms in this patient?**

*HSA would like to thank Dr Ding Ruojun and Dr Nigel Fong Jie Ming from Department of Renal Medicine at Sengkang General Hospital, for contributing this article.*

Answers can be found on page 8.

## One-stop access to trusted drug information: National Drug Formulary

The National Drug Formulary (NDF) is a national drug information website for healthcare professionals established under the National Pharmacy Strategy. It consolidates product information from HSA's Therapeutic Products Register, post-marketing information and educational materials, Ministry of Health (MOH) drug subsidy status and drug guidances, and information on the general availability of medicines across public healthcare institutions. By bringing these resources together in one place, NDF supports medicine-related decision-making across prescribing, dispensing, administration and monitoring. Launched in April 2022, NDF is intended for use across multiple care settings and can be accessed at www.ndf.gov.sg.

### What healthcare professionals can find in NDF

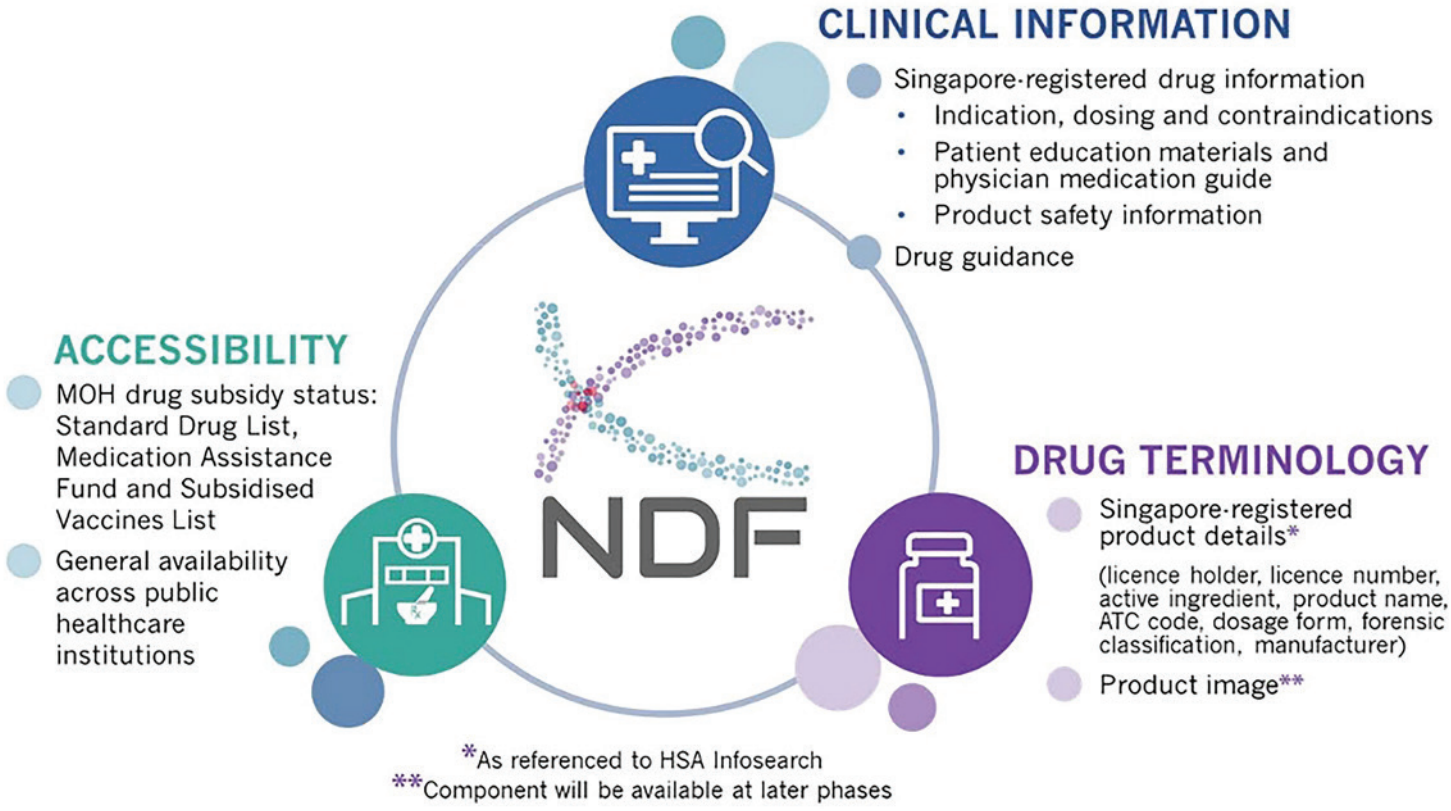



Figure 1. The core components of NDF

- **Product and clinical information:**
  HSA-approved therapeutic product information including active ingredient(s), forensic classification, indications, dosing and contraindications.
- **Safety and educational resources:**
  Dear Healthcare Professional Letters, and educational materials such as Physician Educational Materials for healthcare professionals and Patient Medication Guides for patients.
- **Subsidy information and guidance:**
  Agency for Care Effectiveness (ACE) drug guidance and MOH subsidy status, including the Standard Drug List, Medication Assistance Fund and Subsidised Vaccine List.
- **General availability information:**
  Information on medicine availability across public healthcare institutions to support medication review and transitions of care.

## A refreshed website for better user experience

The NDF website was refreshed in April 2026 with enhanced search functions and clearer navigation. These improvements help users locate relevant drug pages, product information and supporting resources more efficiently. Figures 2 and 3 highlight selected functions of the refreshed website.

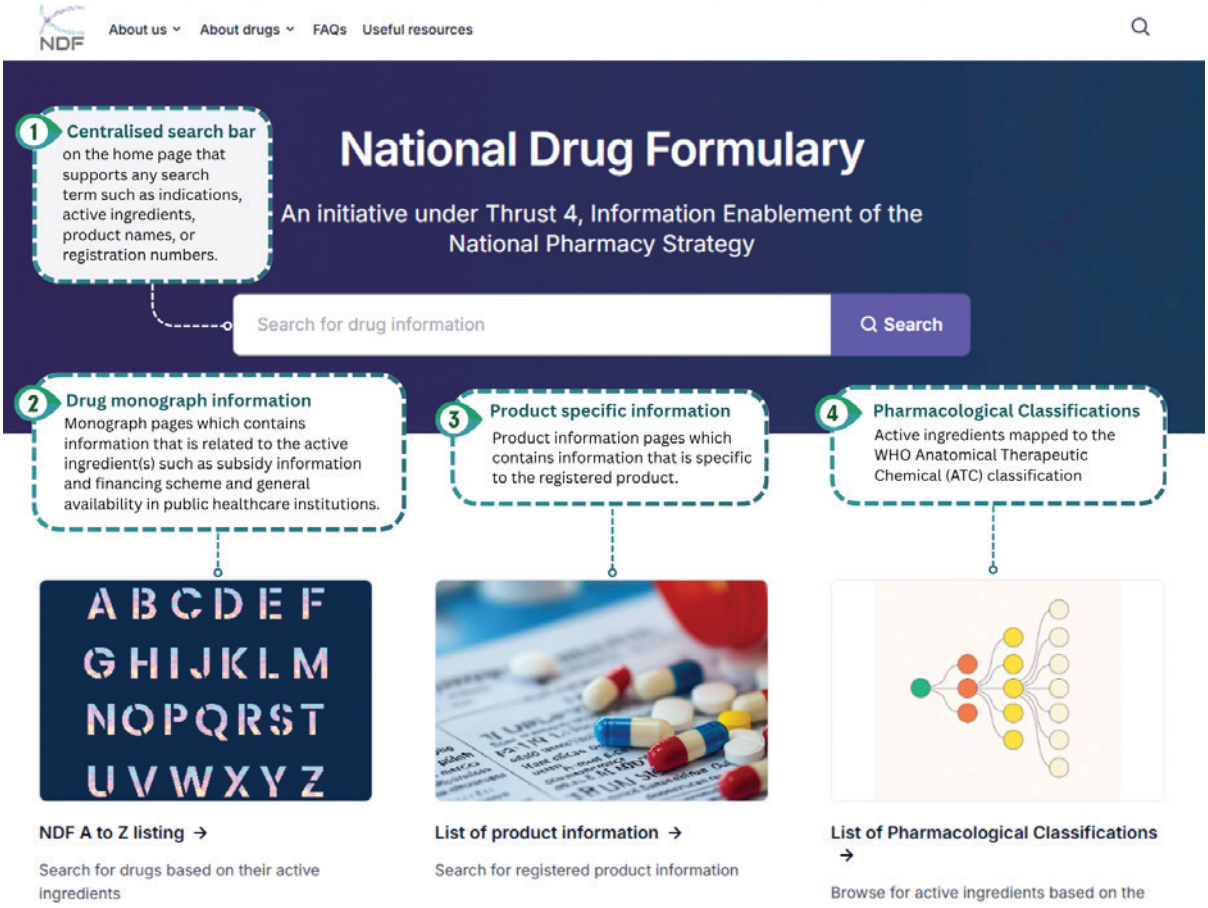



Figure 2. Refreshed NDF home page and navigation

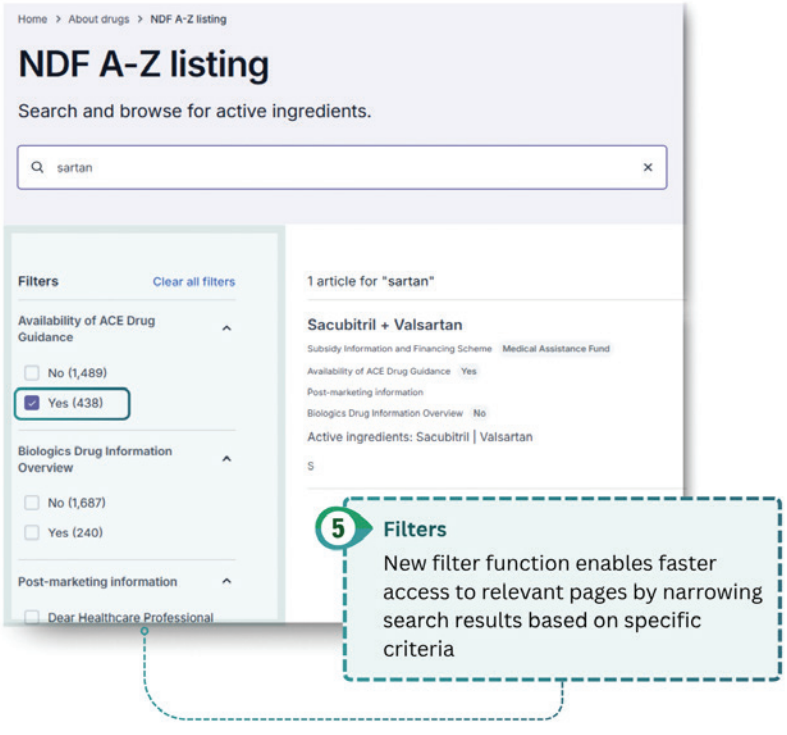



Figure 3. Filter function in the “NDF A to Z listing” and “List of product information” pages

## Visit and explore NDF

Visit www.ndf.gov.sg or use the accompanying QR codes to access the website and user guide.

www.ndf.gov.sg

www.ndf.gov.sg/about-us/ndf-user-guide

## Answer to AE Case in Focus 1: Test Yourself

The recurrent anaphylaxis in this patient was eventually attributed to the use of chlorhexidine topical solution.

The healthcare team systematically excluded other potential triggers for the patient's recurrent anaphylaxis. Ethylene oxide IgE testing was performed and returned negative. Heparin and the dialyser membrane were ruled out based on their consistent use during outpatient dialysis sessions without adverse reactions. Further history taking revealed that chlorhexidine was only used in the inpatient setting and not during outpatient dialysis. Chlorhexidine IgE testing showed a raised titre, indicating that the patient had developed a specific IgE-mediated hypersensitivity (Type I allergic reaction) to chlorhexidine, supporting it as the likely causative agent. The patient was advised to avoid chlorhexidine in the future, and a chlorhexidine allergy was documented in his medical records to alert future healthcare providers. He tolerated subsequent inpatient dialysis sessions without any allergic reaction.

### About chlorhexidine allergy

Chlorhexidine is a broad-spectrum antiseptic effective against bacteria on the skin. It is present in many topical and oromucosal antiseptic products, such as creams, wipes, cleansers, mouthwashes, contact lens solutions, lozenges, topical anaesthetics, and antimicrobial dressings. Certain indwelling catheters — including urinary and central venous catheters — may also be coated or impregnated with chlorhexidine to help prevent infections.[1,2] Identifying chlorhexidine allergy can be challenging, given that exposure to chlorhexidine may occur through a wide range of sources. Chlorhexidine is also a frequently overlooked allergen in the perioperative setting where it is commonly used as a skin antiseptic before surgery or during the insertion of needles and lines. Although allergic reactions to chlorhexidine are rare, they are increasingly being recognised.

### Local situation

As at 1 September 2026, HSA has received 95 reports of anaphylaxis associated with chlorhexidine. This represents a notable increase from the 15 cases of anaphylaxis in 2017, when HSA issued a safety communication on the risk of serious allergic reactions, including anaphylactic reactions, with chlorhexidine.[3] This trend may reflect growing clinical awareness of chlorhexidine as a potential allergen, improved recognition and reporting of hypersensitivity reactions, and the increasing use of chlorhexidine-containing products in healthcare settings. Of the 95 reports, patients ranged in age from 16 to 87 years, with males (n=54) accounting for the majority. Twenty-nine cases were reported with other co-suspected medicines, the most common being atracurium, cefazolin, lidocaine, bupivacaine and midazolam — all of which are drugs frequently used in the peri-operative setting. Twenty-three cases had chlorhexidine confirmed as the culprit agent following allergy testing via skin prick test (15 cases), intradermal test (4 cases), both methods (2 cases), or an unreported test type (2 cases).

Aside from the case cited in this article, two other cases of anaphylaxis during haemodialysis were reported to HSA, both involving women in their sixties. Both patients experienced repeated anaphylactic or hypersensitivity episodes during their dialysis sessions in which chlorhexidine was used as a cleansing agent. Chlorhexidine was subsequently identified as the culprit via skin prick or intradermal tests in both cases.

### HSA advisory

Chlorhexidine is widely used in the preparation process for dialysis in the inpatient setting and perioperative procedures, and is present in many products which are readily available over the counter. Despite its ubiquity, anaphylaxis caused by chlorhexidine remains rare and, as a result, may often not be considered as the causative agent in the initial stages of assessment. Anaphylaxis occurring during dialysis presents a complex diagnostic challenge because patients are exposed to multiple potential allergens simultaneously, making identification of the causative agent difficult.

Healthcare professionals are reminded to remain vigilant and to consider chlorhexidine as a hidden culprit in cases of peri-procedural anaphylaxis. Such cases may warrant a referral to an allergist to ascertain the cause of the anaphylaxis.

#### References


1. *Br J of Anaesth 2019; 123: e95–103*
2. *Allergo J Int 2025; 34: 271–5*
3. *https://www.hsa.gov.sg/announcements/safety-review-on-risk-of-serious-allergic-reactions-with-chlorhexidine/*


# Answer to AE Case in Focus 2: Test Yourself

This patient's neurological symptoms were attributed to neurotoxicity from aciclovir accumulation. A temporary femoral haemodialysis catheter was urgently inserted for haemodialysis in view of the severity of her neurological symptoms. Her symptoms improved significantly after one session of haemodiafiltration and completely resolved after a second session. She was restarted on her routine peritoneal dialysis prescription and was discharged well after. Aciclovir was not restarted as it was no longer necessary, given that her shingles symptoms were minimal.

## Aciclovir-induced neurotoxicity in patients on peritoneal dialysis

Aciclovir is an acyclic guanosine nucleoside analogue indicated for the treatment of herpes virus infections. Approximately 60% to 90% of the drug is excreted unchanged by the kidneys via glomerular filtration and tubular secretion, and its clearance is greatly reduced in patients who have renal impairment. The half-life of aciclovir is 2 to 3 hours in individuals with normal kidney function and 20 hours in patients with end-stage renal disease.[1] As such, aciclovir has a high potential for accumulation and neurotoxicity when unadjusted doses are given to patients with renal impairment, particularly those on peritoneal dialysis where aciclovir clearance is poor. In this patient, the recommended dose is 800mg twice daily at approximately twelve-hourly intervals.

Aciclovir-induced neurotoxicity can present as confusion, neuropsychiatric symptoms, dysarthria, myoclonus, and even seizures.[2] In dialysis patients presenting with confusion, such as in this case, the differential diagnosis can be broad, including stroke, meningoencephalitis, sepsis, electrolyte abnormalities, and drug toxicity. Hence, a holistic clinical assessment and workup is essential. In this case, varicella-zoster virus meningoencephalitis was deemed less likely, given the localised zoster vesicles and the lack of systemic signs of infection. In cases where it is difficult to ascertain the cause of the confusion, a lumbar puncture may be warranted to exclude infectious causes.

## Management of aciclovir-induced neurotoxicity

In addition to stopping the offending drug, haemodialysis/haemodiafiltration is also used for acute management of aciclovir neurotoxicity in peritoneal dialysis patients. Due to its low molecular weight (225 Daltons), low protein binding (9–33%), low volume of distribution (0.6 L/kg), and high water-solubility, aciclovir is efficiently cleared by haemodialysis. A standard 4-hour session of haemodialysis removes approximately 50–60% of body aciclovir.[1] In comparison, peritoneal dialysis, which provides slow continuous solute removal, is less efficient in removing aciclovir, with a 24-hour session of continuous ambulatory peritoneal dialysis treatment removing only less than 10% of body aciclovir.[3]

## Local situation

As at 1 September 2026, HSA has received 11 adverse event (AE) reports of neurotoxicity or symptoms suggestive of neurotoxicity associated with the use of aciclovir. The AEs included encephalopathy, altered mental state, cerebellar syndrome and delirium. Eight patients were female and three were male, with a median age of 74 years (range 41–89 years). Five patients were hospitalised. Four patients were reported to have recovered, while the outcomes of the remaining patients were unknown at the time of reporting. Notably, three patients had a background of end-stage kidney disease managed with peritoneal dialysis, of whom one developed symptoms of neurotoxicity despite being given a renally-adjusted dose of aciclovir.

Neurological effects are known AEs of aciclovir and are listed in the package inserts of locally registered aciclovir-containing products. Common neurological AEs include headache and dizziness, while agitation, confusion, tremor and ataxia are some of the rarely reported AEs.[4] Close monitoring of elderly patients and patients with renal impairment is recommended as they are at higher risk of developing neurological AEs. These reactions are generally reversible upon discontinuation of treatment.

## HSA's advisory

This case highlights the importance of dose adjustment for renally cleared medications such as aciclovir in patients on peritoneal dialysis. Determining the appropriate renal dose for such patients could be complex, and the appropriate renal dose may not always be apparent at the point of prescribing. Regardless, healthcare professionals are encouraged to be vigilant when prescribing aciclovir by considering the patient's renal function prior to initiation. Healthcare professionals are encouraged to report suspected aciclovir-induced AEs such as neurotoxicity to the Vigilance and Compliance Branch of HSA.

### References


1. *Am J Case Rep. 2018 Dec 9; 19: 1459–62*
2. *J Clin Pharm Ther. 2021 Aug; 46(4): 918–26*
3. *Am J Kidney Dis. 1986 Jun; 7: 507–10*
4. *Singapore package insert for Zovirax. Approved 3 November 2025.*





Please send your enquiries, comments and suggestions to:

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