ISSN: 0219 - 2152 May 2026 Vol.28 No.1

ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

Scan / click the QR code to read the full issue online

Biosimilars: Transforming healthcare through enhanced patient access — Pg 3

- Biosimilars are highly similar biological medicines to their reference biologics. They improve patient access to effective treatments while managing costs.
- HSA has a robust regulatory framework for biosimilar approval to ensure therapeutic equivalence. Experience from post-market surveillance also help support the comparable safety profiles of biosimilars to reference biologics.
- Real-world data from the Agency for Care Effectiveness (ACE) shows strong clinical acceptance of use of biosimilars locally with substantial healthcare savings.
- HSA and ACE have co-developed a patient factsheet to assist doctors in discussing treatment options with their patients.

Analysis of adverse event reports for year 2025 — Pg 4 - 7

- In 2025, HSA received 15,285 valid adverse event (AE) reports.
- The top five pharmacotherapeutic product groups suspected of causing AEs were antibiotics, nonsteroidal anti-inflammatory agents, analgesics, drugs used in diabetes, and lipid-modifying agents.
- There were 357 vaccine adverse event (VAE) reports, including 28 COVID-19 VAE reports. Commonly reported AEs with childhood vaccines in children below 12 years included lymphadenopathy (suppurative and non-suppurative) and injection-site reactions with the *Bacillus Calmette-Guérin* (BCG) vaccine and seizures (febrile and afebrile) with various vaccines. Commonly reported VAEs in adults were hypersensitivity reactions and injection site reactions with various vaccines.
- There were 66 AE reports associated with complementary health products and cosmetics, with allergic reactions associated with glucosamine-containing products and melatonin-containing products being the most commonly reported.

AE Case in Focus: Test Yourself — Pg 7 - 8

A male in his early 50s presented to the outpatient clinic for his regular medical consultation. He had a medical history of hypertension, hyperlipidaemia, prior vitamin B12 and iron deficiency anaemia, and chronic urticaria. His long-term medicines included telmisartan, nifedipine, ferrous gluconate and mecobalamin. He had also been taking cetirizine daily for the past two years for persistent pruritus and allergic symptoms. The patient attempted to discontinue cetirizine twice but developed extensive erythematous wheals over the trunk and bilateral forearms accompanied by severe generalised pruritus within several days of each cetirizine discontinuation attempt. The pruritus was persistent, affecting his sleep and impairing daily function. There were no identifiable alternative triggers. Reintroduction of cetirizine led to rapid improvement of pruritus and resolution of urticarial lesions within two to three days.

What could have caused the sudden and severe recurrence of pruritus and urticaria in this patient?

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

List of Dear Healthcare Professional Letters on therapeutic product safety concerns issued by HSA and pharmaceutical companies in 2025

For details of each DHCPL, please log on to MOH Alert via your professional board's website.

Date of issuance	Therapeutic product safety concern
25 March 2025	**Elevidys™ (delandistrogene moxeparvovec)** Updates and new measures related to risk of acute liver failure following treatment
10 June 2025	**Opzelura® 15 mg/g cream (ruxolitinib phosphate)** Possible presence of small, visible crystal-like particles in product
11 June 2025	**Proluton Depot Injection 250mg/ml** Update on benefit-risk balance and discontinuation in supply, following assessment outcome for hydroxyprogesterone (17-OHPC)-containing medicinal products by the Pharmacovigilance Risk Assessment Committee in the European Union
23 June 2025	**Elevidys™ (delandistrogene moxeparvovec)** Discontinuation of dosing in non-ambulatory Duchenne Muscular Dystrophy patients, irrespective of age, following a second overseas case of fatal acute liver failure
11 July 2025	**Cellcept (mycophenolate mofetil)** New risk of anaphylactic reaction identified from post-marketing data
28 July 2025	**Ocrevus® (ocrelizumab)** New identified risk of clinically significant liver injury without findings of viral hepatitis
25 August 2025	**Bepraz Gastro Resistant Tablet 20mg (rabeprazole)** Voluntary consumer level recall of product due to detection of low levels of an impurity, a degradation by-product of the active ingredient rabeprazole sodium, in one batch of Bepraz
1 September 2025	**Lipidem® 200mg/ml Emulsion for Infusion (10 x 500 ml)** Detection of subvisual droplet-like structures of emulsion components in the product, with advice to use a lipid emulsion filter until further notice
5 September 2025	**Polivy (polatuzumab vedotin)** New identified risk of infusion site extravasation
15 September 2025	**Jinarc® (tolvaptan)** Update on the Risk Management Plan to streamline the supply process
12 November 2025	**Yescarta® (axicabtagene ciloleucel)** Risk of cerebral oedema in patients with primary mediastinal B cell lymphoma

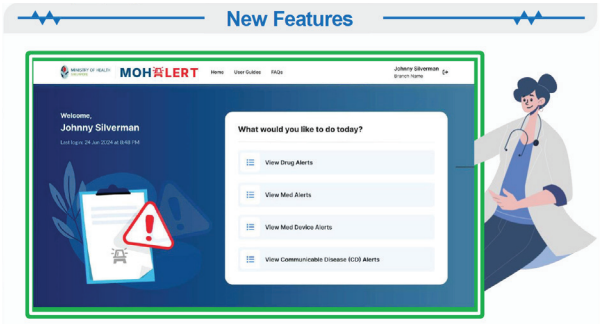
Upgraded MOH Alert Portal

On 31 January 2026, the Ministry of Health launched an upgraded MOH Alert portal for healthcare professionals. This platform continues to serve as a crucial communication tool for the Ministry of Health and its agencies to share important updates with the healthcare community. Healthcare professionals can access the portal to view Dear Healthcare Professional Letters and product safety alerts issued by HSA.

The newly revamped portal introduces several key improvements:

- **Enhanced Accessibility:** A responsive web design coupled with seamless login through SingPass.
- **Expanded Content:** New specialised alert categories, such as Medical Device and Communicable Disease Alerts.
- **Improved Navigation:** An upgraded search function that incorporates filters for easier access to previous alerts.

Dear Healthcare Professional Letters on safety concerns



Healthcare professionals can access the updated system at https://de-rom.moh.gov.sg/mohalert

If you have any questions or require support, you can contact moh_alert@moh.gov.sg.

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 May 2026.

Biosimilars: Transforming healthcare through enhanced patient access

The healthcare landscape is evolving rapidly, with biological medicines being used increasingly to treat complex conditions, from cancer to autoimmune diseases. As clinicians navigate the delicate balance between providing optimal patient care and managing healthcare costs, increased knowledge of biosimilars can improve treatment accessibility without compromising clinical standards. In view of this, HSA and the Agency for Care Effectiveness (ACE) have collaborated to build clinical confidence and encourage biosimilar adoption by healthcare professionals through various initiatives.

Understanding biosimilars

Biosimilars represent a significant advancement in pharmaceutical science — highly similar biological medicines that demonstrate no clinically meaningful differences in safety and efficacy compared to their reference biologics. Unlike chemical drugs which are relatively simpler chemical molecules, biologics are complex products derived from living organisms. This complexity and inherent variability necessitate sophisticated manufacturing processes and rigorous regulatory oversight to ensure therapeutic equivalence in the case of biosimilars.

When the patents of innovator biologics expire, biosimilar manufacturers can develop follow-on copies using advanced analytical technologies and comprehensive comparability studies. These copies retain therapeutic benefits of the original whilst introducing competitive pricing that enhances affordability.

Regulation of biosimilars to ensure clinical confidence

In 2019, the International Coalition of Medicines Regulatory Authorities (ICMRA) of World Health Organisation (WHO) released a statement on biosimilars to provide assurance on the robust regulatory processes for the approval and monitoring of these medicines to support their global adoption.[1]

In Singapore, HSA has a robust regulatory framework for biosimilar approval. Pharmaceutical companies must demonstrate that their biosimilar is highly similar to the reference biologic through extensive analytical, structural and functional characterisation, supported by targeted non-clinical and clinical comparability studies. Advances in high-resolution analytical technologies now enable precise biosimilar characterisation, complemented by sensitive pharmacokinetic/pharmacodynamic assessments, which allow manufacturers to demonstrate comparability without additional clinical efficacy studies for certain well-characterised biologic products (e.g., G-CSFs, insulin analogues, teriparatide), subject to regulatory assessment. This reflects growing confidence in modern analytical and functional methods to determine comparability between biosimilars and innovator biologics.

For a biosimilar to be registered by HSA, it must have obtained prior approval in at least one major overseas jurisdiction which includes Australia, Canada, Europe, Switzerland, UK and the US. This ensures that biosimilars have already met international standards before local approval. After registration, post-market surveillance ensures their continued safe use locally. HSA is also building its capabilities to evaluate biosimilars de novo in the next few years to enable faster local access to cost effective biologics.

Real-world data of biosimilar adoption and enhanced patient access

Real-world data has established that some biosimilars have been well accepted by clinicians, with substantial cost-savings to the healthcare system. Biosimilars have been available for use in Singapore since 2009 with the approval of SciTropin A™ (somatropin). Since 2018, the Ministry of Health (MOH) has subsidised biosimilar treatments across oncology, rheumatology, gastroenterology, and dermatology.

In a study conducted by the ACE, acceptance and use of biosimilars by clinicians in public healthcare institutions (PHIs) have been high.[2] As the first monoclonal antibody biosimilar to receive subsidy listing in Singapore, infliximab biosimilar achieved over 80% utilisation volume^ within two years. Subsequent biosimilars – rituximab, adalimumab and bevacizumab biosimilars – each achieved more than 95% utilisation volume^ within the first year of subsidy listing. The total number of patients receiving treatment with the five monoclonal antibodies (infliximab, adalimumab, trastuzumab, rituximab and bevacizumab) in PHIs increased from 1,800 to nearly 4,100* over four years.

Despite the significant increase in patient numbers receiving treatment, overall spending for these five monoclonal antibodies decreased by more than half, from approximately $57 million in 2018 to $25 million in 2022. This resulted in cumulative cost savings of approximately $136 million over five years. More biosimilars with competitive prices are expected to enter the market, thereby improving patient access to affordable treatment options.

^Calculated by the utilisation volume in Prescribed Daily Dose (PDD) of the biosimilar over the total utilisation volume of the reference biologic and biosimilar.
**Absolute patient numbers receiving treatment*

Experience from post-market surveillance of biosimilars

HSA maintains comprehensive post-market surveillance of biosimilars approved for use in Singapore through its national pharmacovigilance system. To date, HSA's monitoring of local adverse event reports and global surveillance efforts have not identified any additional safety signals specific to biosimilar products. This contributes to supporting their comparable safety profile to reference biologics in real-world clinical practice. Together with the stringent regulatory requirements for biosimilar approval and the accumulated knowledge from evidence-based literature, this provides reassurance that biosimilars demonstrate no clinically meaningful differences in safety and efficacy.[3,4] In addition, HSA is building capabilities to test the potency and quality of biosimilars used in our population, which will further enhance confidence in their use.

Conclusion

The availability of safe and efficacious biosimilars enables clinicians to provide care to more patients whilst maintaining high therapeutic standards. HSA and ACE have jointly developed a patient factsheet on biologics and biosimilars. This resource also provides information about subsidised biosimilars for various medical conditions, so that doctors can discuss suitable treatment options with their patients.

References

1. http://www.icmra.info/drupal/sites/default/files/2019-07/ICMRA_statement_about_confidence_in_biosimilar_product_HCP.PDF
2. *Pharmacoecon Open 2024; 8: 679–88*
3. *J Clin Med 2025; 14: 1644*
4. *Blood 2012; 120: 5111–7*

We would like to thank our colleagues from the Agency for Care Effectiveness (ACE) for contributing to this article.

Analysis of adverse event reports for year 2025

Key Points

- In 2025, HSA received 15,285 valid adverse event (AE) reports.
- The top five pharmacotherapeutic product groups suspected of causing AEs were antibiotics, nonsteroidal anti-inflammatory agents, analgesics, drugs used in diabetes, and lipid-modifying agents.
- There were 357 vaccine adverse event (VAE) reports, including 28 COVID-19 VAE reports. Commonly reported AEs with childhood vaccines in children below 12 years included lymphadenopathy (suppurative and non-suppurative) and injection-site reactions with the *Bacillus Calmette-Guérin* (BCG) vaccine and seizures (febrile and afebrile) with various vaccines. Commonly reported VAEs in adults were hypersensitivity reactions and injection site reactions with various vaccines.
- There were 66 AE reports associated with complementary health products and cosmetics, with allergic reactions associated with glucosamine-containing products and melatonin-containing products being the most commonly reported.

This is a review of AE reports received by HSA in 2025. The scope of this review includes pharmaceuticals (i.e., chemical drugs, biologics, vaccines), cell, tissue, and gene therapy products (CTGTP), complementary health products (CHPs) and cosmetic products.

Report analysis for 2025

(a) Volume of reports

HSA refined its processing criteria for local reports received in 2025 to further strengthen the AE database and optimise signal detection capabilities. This resulted in a total of 15,285 valid[+] reports received in 2025, which was lower than the 25,141[+] reports received in 2024 and the average annual volume of 24,678 reports received for the past 10 years (i.e., 2015 to 2024). Hence, this lower volume of reports does not indicate a poorer reporting rate but instead translates to reports of higher value to our national AE database.

[+]Reports include COVID-19 vaccine AE reports. Reports lacking important details such as names of suspected drugs and AE descriptions were regarded as invalid reports and were not captured into the national AE database as these could not be assessed for causality.

(b) Types and sources of reports

Majority of the reports were associated with pharmaceuticals (99.5%)*, which included chemical drugs (95.1%), vaccines (2.2%), and biologics (2.2%). This was followed by CHPs (0.4%), which included Chinese Proprietary Medicines[‡], health supplements and traditional medicines. The remaining reports were associated with CTGTP (0.1%) and cosmetic products (0.03%).

**Figures may not add up to 100% due to rounding*

[‡]Chinese Proprietary Medicines are medicinal products in the form of finished products, such as capsules or tablets, that contain one or more active ingredients from plants, animals, or minerals documented for use in traditional Chinese medicine.

Most of the AE reports were from public hospitals (62.3%), followed by polyclinics (23.6%). Other reporting sources included GP clinics (9.6%), product registrants (3.2%), private hospitals (0.4%), private specialist clinics (0.2%), and public (0.2%) and private nursing homes/community hospitals (0.2%). Doctors (88.4%) contributed the highest number of reports, followed by pharmacists (5.1%) and drug companies (3.2%). The remaining groups of reporters were dentists, nurses and research coordinators.

(c) Demographics

Where patient demographics were reported, two-thirds of the AE reports received were for females (61.4%). Chinese patients constituted the highest proportion (73.4%) of AE reports, followed by Malays (16.8%), Indians (6.6%), Eurasians (0.3%) and others (2.9%). The majority of AEs occurred in adults (18 years and above, 94.4%), followed by children (below 12 years, 3.6%) and adolescents (12-17 years, 2.0%).

AE reports associated with chemical drugs, biologics and CTGTP

The top five drug classes suspected of causing AEs were from the following pharmacotherapeutic groups: antibiotics (28.1%), nonsteroidal anti-inflammatory drugs (NSAIDs) (17.6%), analgesics (7.3%), drugs used in diabetes (4.7%), and lipid-modifying agents (4.3%). Refer to Figure 1 for the breakdown of the top three drugs within each of the top five drug classes.

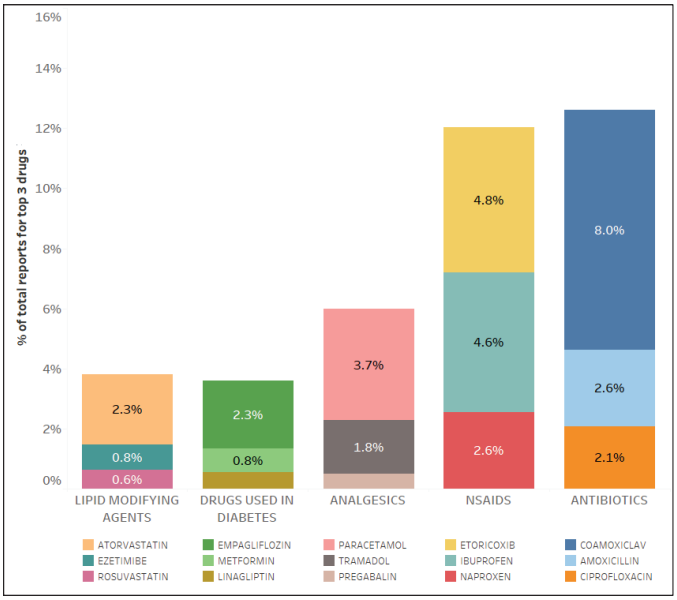
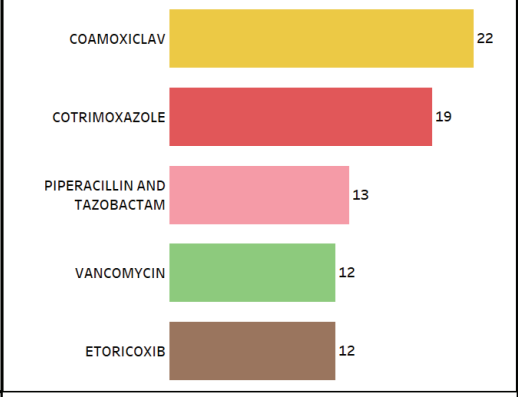
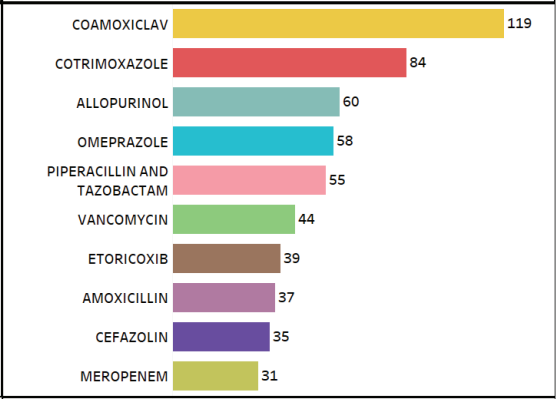
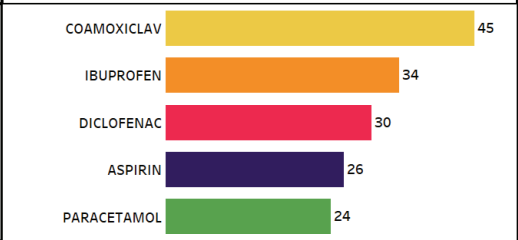
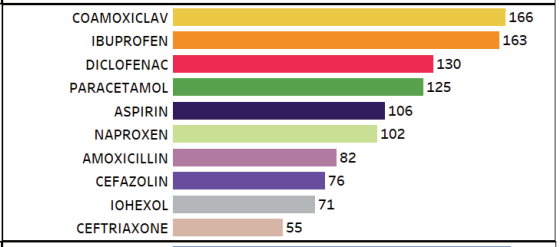
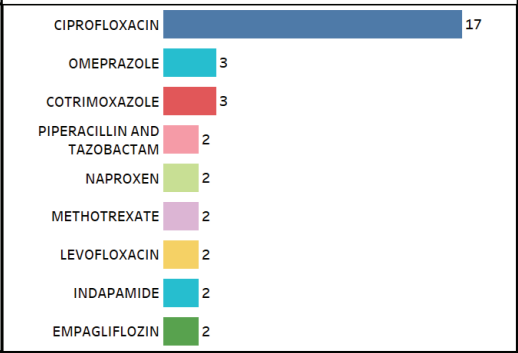
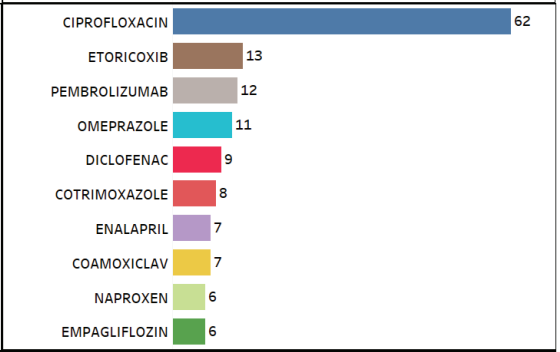
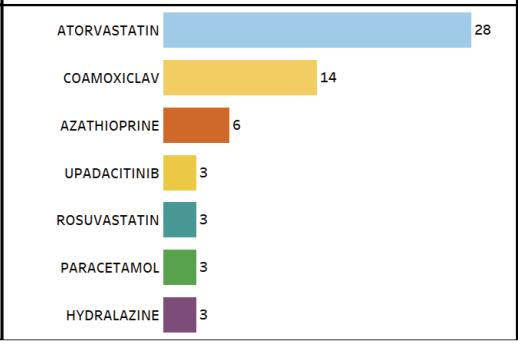
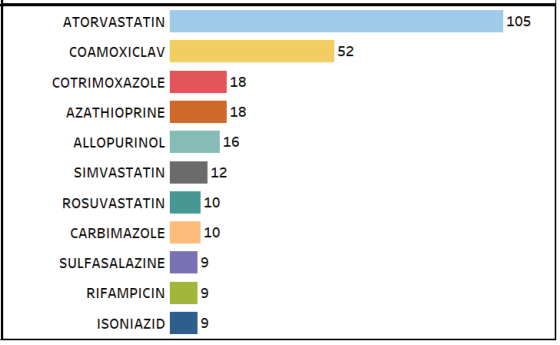


Figure 1. Top 5 drug classes and the top 3 drugs within each drug class (by active ingredients) suspected of causing AEs

A large proportion of AEs reported were skin and subcutaneous tissue disorders (56.2%), followed by eye disorders (e.g., periorbital or eyelid oedema, oculogyric crisis) (10.0%), and general disorders and administration site conditions (e.g., face oedema, mucosal ulceration, leg oedema, fever) (9.2%). Most of the AE reports described non-serious reactions such as rash, pruritus, and angioedema. The top five active ingredients suspected to cause serious AEs of interest in 2025 are summarised in Table 1.

Table 1. Top active ingredients suspected to cause serious AEs of interest in 2025, in comparison to the period 2021 to 2025[x]

Description	Top 5 suspected active ingredients in 2025	Top 10 suspected active ingredients from 2021-2025 (Based on cumulative number of times the active ingredients were implicated from 2021-2025)
Severe cutaneous adverse reactions (SCARs) (Acute generalised exanthematous pustulosis (AGEP), Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN))		
Anaphylactic Reaction		
Renal disorders (Autoimmune renal disease, Glomerulonephritis, Kidney infection, Nephritis interstitial, Renal artery stenosis, Renal atrophy, Renal failure acute/chronic, Renal tubular disorder/necrosis, Toxic nephropathy)		
Hepatic disorders (Acute on chronic liver failure, Autoimmune hepatitis, Cholestatic liver injury, Chronic hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis, Hepatitis cholestatic, Hepatotoxicity, Jaundice)		

[x]More than 5 or 10 active ingredients may be displayed in each column respectively if the number of reports of these active ingredients is the same.

It is worth noting that these figures do not take into consideration the drugs' utilisation rates and therefore do not inform on their relative safety profiles. More than one drug may be implicated in a single AE report. Overall, the AEs associated with the implicated drugs are generally consistent with the known safety profile of these drugs.

Vaccine AE reports

In 2025, HSA received 357 vaccine adverse event (VAE) reports, of which 28 (7.8%) reports were suspected to be associated with COVID-19 vaccines[†]. 116 (32.5%) reports involved adults, and 241 (67.5%) reports involved children and adolescents aged 17 and below. Most of the paediatric reports were received from the active surveillance site at KK Women's and Children's Hospital (n=222, 92.1%), which HSA partners with to screen paediatric hospital admissions for post-vaccination AEs.

[†]COVID-19 vaccines are mRNA vaccines (Comirnaty® and Spikevax®)

(a) VAEs in children and adolescents

In children below 12 years, the commonly reported VAEs were lymphadenopathy (suppurative and non-suppurative) and injection-site reactions with the Bacillus Calmette-Guérin (BCG) vaccine, as well as seizures (febrile and afebrile) with various vaccines. Seizures were most frequently reported with measles, mumps and rubella (MMR), varicella, measles, mumps, rubella and varicella (MMRV), 5-in-1[#], 6-in-1^, pneumococcal conjugate and influenza vaccines. Kawasaki Disease was reported with various vaccines and often occurred concurrently with infections. Other VAEs reported in this age group included allergic reactions such as urticaria and angioedema, vaccination failure, thrombocytopenia, meningitis, *Henoch-Schönlein* purpura, and transient synovitis.

Among adolescents aged 12–17 years, common VAEs reported included rash or vaccination failure with hepatitis B, pneumococcal, and influenza vaccines. Individual reports

comprised acute generalised exanthematous pustulosis with hepatitis B vaccine, thrombocytopenia and arthritis with human papillomavirus (HPV) vaccine, and events of seizure, anaphylaxis, *Henoch-Schönlein* purpura, and syncope with influenza vaccines. There was also one isolated case of appendicitis with COVID-19 vaccine.

#5-in-1 refers to Diphtheria, Pertussis, Tetanus, Inactivated Polio, and Haemophilus Influenza Type B
^6-in-1 refers to 5-in-1 with Hepatitis B

(b) VAEs in adults

The commonly reported VAEs in adults were hypersensitivity reactions such as rash, urticaria, angioedema, dyspnoea, pruritus, and injection site reactions with seasonal influenza, pneumococcal, zoster, HPV and MMR vaccines. Serious VAEs included anaphylaxis with influenza or pneumococcal vaccines. There were also isolated reports of hearing impairment accompanied by high fever, psychosis, and thrombocytopenia suspected to be associated with COVID-19 vaccines.

HSA's review of the VAE reports in 2025 did not identify new safety concerns with the vaccines. Overall, the VAEs received in 2025 were consistent with expected AE frequencies listed in the product package inserts or published in literature.

Complementary health products and cosmetics AE reports

There were 66 AE reports associated with CHPs and cosmetics, with 33 cases (50%) implicating products classified as health supplements. The most commonly reported AEs were allergic reactions such as rash, pruritus and urticaria associated with glucosamine-containing products (n=11, 16.7%) and melatonin-containing products (n=10, 15.2%).

Serious AEs reported with CHPs were rare and included hepatic and renal AEs. No safety concerns were identified for these CHPs, as these were isolated cases and some were confounded by multiple factors, such as the patient's underlying conditions and/or concomitant use of other products.

Several products containing adulterants were detected through AE reports, including:

- "EZ Empire Be Perfect" which contained cyproheptadine and dexamethasone. A female patient took the product daily for about 10 months and experienced increased appetite leading to a weight gain of more than 10 kg, as well as sudden onset of facial rashes and lethargy upon cessation of the product. These symptoms were suspected to be due to Cushing's syndrome and steroid withdrawal.

- "Tong Mai 9 Gu Jiao Rou" which contained dexamethasone and piroxicam. A male patient developed a perforated gastric ulcer requiring emergency surgery and experienced symptoms of Cushing's syndrome after taking the product for about two years.

- "HW Beauty Serbuk Campuran Kurma, Madu & Limau Kasturi" which contained dexamethasone, prednisolone and diclofenac, leading to acute kidney injuries and Cushing's syndrome in some patients.

- "Ubat Angin Tulang" which contained dexamethasone, furosemide and chlorpheniramine causing rapid weight gain and elevated blood pressure in a female patient.

Press releases were issued to warn the public not to consume these products which were purchased online or from dubious sources.[1]

Highlights on local safety signals for the year 2025

HSA conducts regular individual and aggregated reviews of adverse event (AE) reports to detect serious unexpected AEs not listed in the drug's package insert (PI), and known AEs reported more frequently than observed from clinical trials or global post-marketing experience. Any local safety signals and significant drug-AE pairs of interest relevant to the local context will be published in this bulletin to raise healthcare professionals' awareness. These signals may represent preliminary investigations and may not necessarily indicate a confirmed drug safety issue.

In 2025, HSA identified the following local safety signals:

Thyroid disorders following dupilumab therapy

Dupilumab (Dupixent, Sanofi-Aventis Singapore Pte. Ltd.) was registered in Singapore in April 2019. It is a humanised monoclonal antibody indicated for use in several diseases such as atopic dermatitis, asthma and chronic rhinosinusitis with nasal polyposis.

Since 2024, HSA has received three local cases of thyroid disorders temporally associated with dupilumab. The first case involved a 50-year-old female who was diagnosed with Graves' disease following three months of dupilumab therapy for poorly controlled eosinophilic asthma unresponsive to mepolizumab.[2] She had no prior history of thyroid disorder.

The second case was a 60-year-old female who developed Hashimoto's thyroiditis after four months of dupilumab therapy for severe type 2 asthma, and the third case was a 75-year-old male who was detected with hypothyroidism two months after starting dupilumab for chronic obstructive pulmonary disease. His medical history included chronic kidney disease (CKD), peripheral arterial occlusive disease, hypertension and gout.

Thyroid disorders are currently not listed as AEs in the local PI of dupilumab. However, several thyroid conditions associated with dupilumab have been reported in literature, including Graves' disease and Hashimoto's thyroiditis.[3,4,5] HSA initiated a comprehensive review of this potential signal by reviewing data on dupilumab and thyroid disorders from local and overseas reports, international regulators, literature, and the company's assessment report.

A review of local cases noted confounding factors – advanced age, underlying asthma and CKD, or prior exposure to mepolizumab. Asthmatic patients have increased predisposition to autoimmune diseases due to underlying immunological mechanisms.[6-8]

The biological plausability between thyroid disorders and dupilumab remains uncertain. Specifically for autoimmune thyroid diseases such as Graves' disease and Hashimoto's thyroiditis, a potential mechanism has been postulated to be related to the inhibition of the interleukin-4 (IL-4) and interleukin-13 (IL-13) pathways. This suppresses type 2 helper (Th2) T cells which amplifies the type 1 helper (Th1) T cells pathway, increasing Th1 cytokine production. Subsequent increased production of TSH receptor antibodies of the activating subtype leads to Graves' disease.[3] Dupilumab also promotes inflammation towards interleukin-17 (IL-17) and interleukin-23 (IL-23) pathways, which have been implicated in the pathogenesis of Graves' disease.[9,10] In Hashimoto's

thyroiditis, the inflammatory responses driven by the Th1 pathway simultaneously predominate, contributing to the condition's pathogenesis.[4,11]

Despite the postulated mechanism, findings from clinical trials, overseas AE reports and literature showed no clear link between dupilumab and thyroid disorders. No safety concerns on thyroid disorders with dupilumab have been highlighted by international regulatory authorities.

Notwithstanding the lack of confirmatory signals, HSA will continue to monitor this, and update healthcare professionals accordingly.

Cluster of allergic/hypersensitivity reactions with Flebogamma® DIF Solution for Infusion 5%

Human normal immunoglobulin (Flebogamma® DIF Solution for Infusion 5%, Grifols Asia Pacific Pte. Ltd.) is used in primary immunodeficiency syndromes and immunomodulation.

HSA received a cluster of reports on infusion-related allergic/hypersensitivity reactions with Flebogamma® in 21 patients from a local hospital, mostly associated with a specific batch (batch number G04K062631). Four additional cases from another hospital involving the same batch were reported on the same day by the company. Notably, five patients had previously received Flebogamma® without experiencing any AEs.

Within one month, 32 reports from 30 patients were received for Flebogamma® batch G04K062631. Where gender was reported, majority of the patients were females (53.3%). Most patients were above 18 years old (median 46.5 years, range 1–84 years) and had reactions such as urticaria and/or rash. A 72-year-old female developed anaphylaxis requiring hospitalisation.

Due to the cluster reports and involvement of previously tolerant patients, a batch-related issue was suspected. As a precaution, a communication requesting temporary cessation of product use was issued to all purchasers of the product. A subsequent review of the manufacturing process did not uncover any identifiable root cause and analytical test reports of the affected batch were in order.

However, as the estimated incidence of infusion-related AEs for this batch was higher than expected, the company initiated a recall of the affected batch.[12] Subsequent batches of Flebogamma® were closely monitored with no further clusters reported.

Healthcare professionals are encouraged to report any cluster of suspected AEs to the Vigilance and Compliance Branch of HSA even if the reactions are expected, as they may suggest a batch-related issue warranting regulatory actions.

References

1. https://go.gov.sg/hsa-press-releases
2. https://go.gov.sg/adr-news-bulletin-2024-september-vol26-number-2
3. *Endocr Abstracts. 2023; 92: PS3-25-04*
4. *Acta Derm Venereol. 2025; 105: adv41307*
5. *Endocrinol Diabetes Metab Case Rep. 2020: 20-0030*
6. *Eur J Med Res. 2025; 30: 885*
7. *Expert Rev Clin Immunol. 2008; 4: 767–76*
8. *Ann Epidemiol. 2010; 20: 217–22*
9. *J Invest Dermatol. 2022;142: 2660–7*
10. *Endocr J. 2013; 60: 591–7*
11. *Eur J Endocrinol. 2003; 148: 383–8*
12. https://go.gov.sg/recall-of-flebogamma-dif-solution-for-infusion-5

AE Case in Focus: Test Yourself

A male in his early 50s presented to the outpatient clinic for his regular medical consultation. He had a medical history of hypertension, hyperlipidaemia, prior vitamin B12 and iron deficiency anaemia, and chronic urticaria. The patient was taking telmisartan 40 mg every morning, nifedipine (long-acting) 60 mg every morning, ferrous gluconate one capsule daily, and mecobalamin 500 mcg once daily. In addition, he had been taking over-the-counter cetirizine daily for the past two years to control persistent pruritus and allergic symptoms. The patient reported good symptom control of his chronic urticaria while on treatment and had no prior history of other chronic dermatological conditions.

In view of his well-controlled symptoms, the patient attempted to discontinue cetirizine on two separate occasions. He developed extensive erythematous wheals over the trunk and bilateral forearms accompanied by severe generalised pruritus within several days of each cetirizine discontinuation attempt. The pruritus was persistent, resulting in significant sleep disturbance and impaired daily functioning. There were no identifiable alternative triggers, including new medicines, intercurrent infections, or environmental exposures. Reintroduction of cetirizine led to rapid improvement of pruritus and resolution of urticarial lesions within two to three days.

Question: What could have caused the sudden and severe recurrence of pruritus and urticaria in this patient?

HSA would like to thank Dr Benjamin Seng and Dr Prawira Oka from SingHealth Polyclinics for contributing to this article.

Answers can be found on page 8

Answer to AE Case in Focus: Test Yourself

Abrupt discontinuation of long-term cetirizine was the suspected cause of this patient's rebound pruritus and urticaria. A structured withdrawal approach was adopted – switching cetirizine to loratadine 10 mg every morning and chlorpheniramine 4 mg every night for three days, then transitioning to an "as needed" basis. This strategy resulted in successful discontinuation of chronic antihistamine therapy without recurrence of symptoms.

Cetirizine and levocetirizine: second-generation H1-antihistamines

Cetirizine and its enantiomer levocetirizine are second-generation H1-antihistamines widely used for allergy symptom relief. These agents selectively bind to peripheral H1 histamine receptors to block histamine release, resulting in better adverse effect profiles than first-generation antihistamines.

Rebound pruritus and urticaria upon cessation of chronic cetirizine or levocetirizine use

Rebound pruritus and urticaria are increasingly recognised adverse events (AEs) following abrupt discontinuation of cetirizine/levocetirizine. In May 2025, the US Food and Drug Administration (US FDA) issued a Drug Safety Communication on the risk of rare and severe itching upon stopping long-term cetirizine/levocetirizine.[2] Several overseas case reports and pharmacovigilance analyses describe intense pruritus, with or without urticaria, occurring within days of stopping long-term cetirizine/levocetirizine therapy, with duration ranging from months to years.[3, 4]

A study analysing 146 cases of pruritus occurring after cetirizine discontinuation in the US FDA Adverse Event Reporting System database and medical literature suggested a positive association,[4] though this remains rare. Median duration of cetirizine use prior to discontinuation was 24 months (range 0.3 –172.2 months). Another US FDA evaluation of cases revealed that while most patients experiencing rebound pruritus had used cetirizine for more than three months, some experienced this reaction within one month of use.[2] Prolonged continuous use of cetirizine/levocetirizine was identified as a potential risk factor. Female patients were disproportionately affected, comprising 75.3 % of cases.[4]

Symptoms were often severe, generalised, and disproportionate to the patient's baseline allergic condition. Medical interventions were frequently required, with significant impact on quality of life and functional ability.[2] Median time to onset of pruritus from discontinuation was two days (range 0.5–5 days).[4] Rechallenge with the same antihistamine typically led to rapid symptom resolution, with symptom reappearance following subsequent discontinuation.

The exact mechanism of rebound pruritus and urticaria remains unclear. Proposed hypotheses include upregulation or increased sensitivity of H1 receptors during prolonged antihistamine exposure, leading to exaggerated histamine-mediated responses following drug withdrawal.[3] This phenomenon appears to be drug-specific, with more frequent reports with cetirizine/levocetirizine than other antihistamines. The high H1-receptor occupancy and shorter half-lives of cetirizine/levocetirizine may explain the increased likelihood of withdrawal phenomena upon sudden discontinuation, as quick transition from high receptor blockade to rapid drug clearance may trigger rebound pruritus and urticaria.[3]

Management

Rebound pruritus and urticaria are rare but severe, and may lead to significant patient distress, reduced quality of life and functional ability,[2] and unintentional long-term antihistamine dependence. Distinguishing rebound symptoms from flares of patients' underlying allergic conditions may be challenging. Careful clinical assessment is essential, with consideration of the timing of symptom emergence relative to treatment cessation. Awareness of this AE may help practitioners identify cases and avoid unnecessary therapy escalation.

Management strategies include re-initiation of cetirizine/levocetirizine followed by gradual dose tapering, temporary substitution with alternative antihistamines, and short-term corticosteroids.[4,5] Although current evidence is limited, symptom resolution has been achieved with drug re-initiation and subsequent dose tapering. Patients on long-term cetirizine/levocetirizine may be counselled on this risk and reminded to consult healthcare professionals if they experience severe itching after stopping these medicines.[2]

Local situation

Locally, cetirizine is available as General Sale List and Pharmacy Only medicines. Levocetirizine is a prescription-only medicine with exemption for supply without prescription by pharmacists in restricted quantities. Warnings of possible pruritus upon drug discontinuation are listed in the patient information leaflet and package insert of cetirizine and levocetirizine respectively.[6,7]

To date, HSA has not received other local reports of rebound pruritus and urticaria following discontinuation of long-term cetirizine/levocetirizine therapy.

HSA's advisory

Healthcare professionals are advised to consider rebound pruritus when patients who recently stopped chronic cetirizine/levocetirizine use experience severe itching, with or without urticaria. They are encouraged to report suspected AEs to the Vigilance and Compliance Branch of HSA to support ongoing pharmacovigilance activities.

References

1. *Cureus 2024; 16: e450716*
2. *https://www.fda.gov/safety/medical-product-safety-information/cetirizine-or-levocetirizine-drug-safety-communication-fda-warns-about-risk-severe-itching-after*
3. *Drug Saf Case Rep. 2016; 3:16*
4. *Ther Adv Drug Saf. 2019; 10: 1–8*
5. *Clinical & Experimental Allergy, 2026; 0: 1–10*
6. *Singapore package insert for Zyrtec-R (approved on 29 April 2024)*
7. *Singapore package insert for Xyzal (approved on 27 February 2023)*

Please send your enquiries, comments and suggestions to:

Vigilance and Compliance Branch
Health Products Regulation Group
Health Sciences Authority
11 Biopolis Way, #11-01,
Helios, Singapore 138667

Tel : (65) 6866 1111

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