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ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

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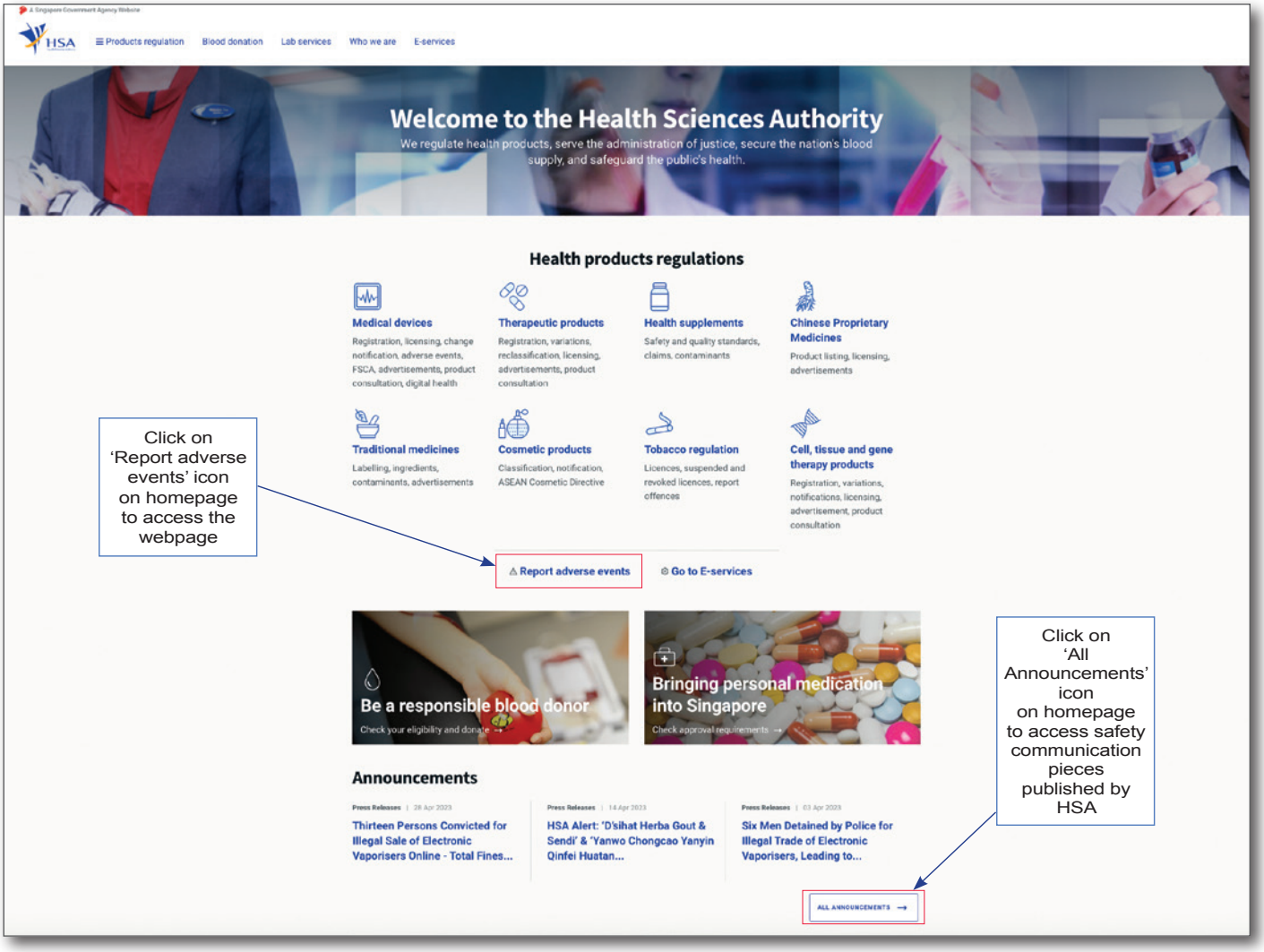

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Dear Healthcare Professional Letters on safety concerns

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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 2023.

Analysis of adverse event reports with COVID-19 therapeutics for the treatment or prophylaxis of COVID-19

Key Points

- As at 31 January 2023, HSA received a total of 62 adverse event (AE) reports associated with COVID-19 therapeutics, i.e., the antivirals and monoclonal antibodies against SARS-CoV-2 virus
- The most commonly reported AEs were largely expected and consistent with the safety data from clinical trials

This is an analysis of adverse event (AE) reports received by HSA for new therapeutics authorised during the COVID-19 pandemic for the treatment or prophylaxis of COVID-19. Broadly, these therapeutics can be classified into two categories: antivirals (i.e., remdesivir, nirmatrelvir/ritonavir and molnupiravir) and monoclonal antibodies (i.e., tixagevimab-cilavimab, sotrovimab and casirivimab/imdevimab).

Adverse events with COVID-19 therapeutics

As at 31 January 2023, HSA received 62 AE reports associated with the therapeutics listed in Table 1. The median age of those who experienced AEs was 78 years (range: 25 to 91 years old), and 80% of the AEs were reported in individuals above 60 years old. The AEs were reported almost equally between males and females.

Table 1. Adverse events reported locally for COVID-19 therapeutics

COVID-19 therapeutics	No of AE reports^ received	Types of AEs (number of events)
Remdesivir (Veklury®)	17	Abnormal hepatic function/hepatic enzymes increased (2), Anaphylaxis (1), Angioedema (2), Arrhythmia (1), Blisters (1), Bradycardia (2), Face oedema (1), Fixed eruption (1), Flushing (1), Hypotension (1), Rash/Urticaria/Pruritus (8)
Nirmatrelvir/ritonavir (Paxlovid™)	29	Acute renal failure (1), Angioedema (2), Blisters (1), Cramps (1), Diarrhoea (3), Disorientation (1), Drug interaction (1), Face oedema (2), Fixed eruption (1), Flushing (1), Giddiness (1), Headache (1), High blood pressure (2), Hypotension (1), Increased transaminases (1), Lack of effect (1), Nausea (2), Off label use (1), Periorbital oedema (1), Rash/Urticaria/Pruritus (13), Rectal bleeding (1), Taste alteration (1), Vomiting (1)
Molnupiravir (Lagevrio)	3	Rash (3)
Tixagevimab-cilgavimab (Evusheld)	1	Anaphylaxis (1)
Sotrovimab	11	Allergic reaction (1), Angioedema (2), Atrial fibrillation (1), Blister (1), Bradycardia (1), Chest pain (1), Chills (1), Decreased oxygen saturation (3), Fever (2), Hypotension (2), Lips swelling (1), Myocardial infarction (2), Rash (1), Shivering (1), Vomiting (1), Wheezing (1)
Casirivimab and imdevimab	2	Chills (2), Fever (2)

^One AE report may contain more than one AE term

1. Intravenous antiviral: Remdesivir (Veklury®)

The AEs of clinical interest from clinical trials data[1] for remdesivir (Veklury®, Gilead Sciences Singapore Pte Ltd) include liver enzyme elevation, renal reactions, infusion-related reactions, respiratory failure, prothrombin time prolongation, and thrombocytopenia. The local AE reports received by HSA were in line with these, with most AEs being allergic reactions such as angioedema, rash and flushing.

In a review conducted by WHO Uppsala Monitoring Centre in 2020 on the spontaneous AE reports of COVID-19 therapies submitted to Vigibase[2], the WHO Global Database of AE reports, remdesivir was the most reported COVID-19-specific therapeutic, appearing in 5,299 of the total 14,574 COVID-19 therapeutic-related AE reports (35.4%), which could be an indicator of its widespread use. While the analysis showed that most of the reported AEs were in line with the known safety profile of remdesivir, certain AEs such as cardiac conditions, hypotension, respiratory conditions and severe hepatic and renal reactions were noted to be disproportionately reported. However, the role of 'confounding by indication' and differences in disease severity in patients treated with remdesivir cannot be completely ruled out, hence further clinical analysis is needed to investigate these potential safety concerns.

2. Oral antivirals: Nirmatrelvir/Ritonavir (Paxlovid™) and Molnupiravir (Lagevrio)

The clinical safety data[3] for nirmatrelvir/ritonavir (Paxlovid™, Pfizer Private Limited) has shown that it was generally well-tolerated, and the incidence of AEs were low. The common AEs of nirmatrelvir/ritonavir reported in clinical trials such as altered sense of taste, diarrhoea, vomiting, hypertension, myalgia and chills, were mild to moderate. Common AEs reported in clinical studies[4] for molnupiravir [Lagevrio, MSD Pharma (Singapore) Pte Ltd] include diarrhoea, nausea and dizziness, and were generally mild.

Locally, HSA received 49 reports associated with these oral antivirals. The most commonly reported AEs were allergic reactions (such as rash, urticaria, pruritus and angioedema) and diarrhoea. Twenty-two AE reports (44.9%) were assessed to be serious and comprised reports of serious allergic reactions including anaphylaxis, acute renal failure, hypotension, bradycardia, disorientation and abnormal hepatic function.

Paxlovid™ has the potential for significant drug-drug interactions due to its ritonavir component, where ritonavir is a strong cytochrome P450 (CYP) 3A4 inhibitor and a P-glycoprotein inhibitor.[5] HSA received a serious report of hypotension arising from a drug interaction between Paxlovid™ and a long-acting calcium channel blocker nifedipine in a 64-year-old male. The patient had been taking nifedipine for hypertension, and three days after initiation of Paxlovid™, he developed hypotension that led to anuric pre-renal acute kidney injury. Although the AE was confounded by the patient's underlying sepsis, the co-administration of Paxlovid™ and nifedipine could have played a contributory role. When nifedipine, a CYP3A4 substrate, is co-administered with Paxlovid™, it can lead to an increase in nifedipine levels which results in adverse events such as hypotension. Drug-drug interaction of calcium channel blockers with Paxlovid™ is listed in the approved package insert of Paxlovid™ and it is recommended that a dose decrease may be needed for these drugs when co-administered with Paxlovid™. Healthcare professionals are reminded to consider the potential drug interactions prior to and during Paxlovid™ therapy and to review the concomitant medications.

3. Monoclonal antibodies

The clinical safety data for monoclonal antibodies such as tixagevimab-cilgavimab (Evusheld, AstraZeneca Singapore Pte Ltd), sotrovimab and casirivimab-imdevimab showed that they were generally well-tolerated with low incidences of AEs.[6,7,8] Common AEs reported in clinical trials for tixagevimab-cilgavimab included headache, throat pain, runny nose, nasal congestion and myalgia, with cardiovascular AEs as one of the AEs of clinical interest.[8]

Fourteen local AE reports were received for the monoclonal antibody therapies. The most commonly reported AEs were infusion-related reactions such as chills, fever, rash, hypotension and decreased oxygen saturation. Eight reports (57.1%) were assessed to be serious which included reports of anaphylaxis, myocardial infarction, hypotension, bradycardia and atrial fibrillation. There was missing information for most of these cases which limited causality assessment.

There were two reports of myocardial infarction that occurred within 48 hours of sotrovimab infusion in two male patients. However, one of the patients had multiple co-morbidities including a cardiac history that could be a potential confounder. For the other patient, there was lack of information to accurately determine the causality as no further follow up information could be obtained from the reporter. Based on currently available local and international information, this potential safety signal is yet to be validated and requires further monitoring.

Conclusion

Based on the local AE reports received with COVID-19 therapeutics, majority were largely expected and in line with their known safety profile reported in clinical trials.

Healthcare professionals are encouraged to look out for AEs that may be associated with therapies used for COVID-19 and to report any suspected serious AEs to the Vigilance and Compliance Branch of HSA.

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Analysis of adverse event reports for health products for year 2022

Key Points

- HSA received 17,870 valid adverse event (AE) reports in 2022 [excluding COVID-19 vaccine adverse event (VAE) reports]
- The top pharmacotherapeutic product groups suspected of causing AEs were nonsteroidal anti-inflammatory agents, antibiotics, analgesics, drugs for cardiovascular system, gastrointestinal agents, and contrast media
- There were 236 VAE reports. In children aged 12 years and below, the most commonly reported VAE was lymphadenopathy with Bacillus Calmette-Guerin (BCG) vaccines. In adults, the most commonly reported AEs were allergic reactions such as rash, angioedema, and injection site reactions with seasonal influenza, hepatitis B, pneumococcal, tetanus, human papillomavirus (HPV), and measles, mumps, and rubella (MMR) vaccines
- There were 71 AE reports associated with complementary health products (CHPs). These included five reports of allergic reactions with probiotic products, of which two were anaphylaxis reports

This is a review of AE reports received by HSA in 2022. The scope of this review includes pharmaceuticals [i.e., chemical drugs, biologics, vaccines and cell, tissue, and gene therapy products (CTGTP)], complementary health products (CHP) and cosmetic products. Reporting patterns which may be of interest are highlighted. COVID-19 vaccine AE reports are excluded in this review as they are separately reviewed and published on pages 5 - 6 of the bulletin.

Report analysis for 2022

(a) Volume, sources, and types of reports

In 2022, HSA received a total of 17,870 valid AE reports* which were lower than the number received in 2021 (21,206). Reports lacking important details such as names of suspected drugs and AE descriptions were regarded as invalid. These were not captured into the national AE database as they could not be assessed for causality. Majority of the reports were associated with pharmaceuticals (99.6%), which included chemical drugs (96.5%), biologics (1.6%), vaccines (1.4%) and CTGTP (0.01%). The AE reports associated with CHPs accounted for 0.4% of the reports, which included Chinese Proprietary Medicines (CPMs), health supplements and traditional medicines. The remaining 0.02% of the reports were associated with cosmetic products.

Similar to past years, most of the AE reports were from the public sector i.e., public hospitals (54.3%), polyclinics (24.2%), public specialist clinics (2.5%), government agencies (1.0%) and nursing homes (0.2%). Other reporting sources included General Practitioner (GP) clinics (13.5%), product registrants (2.8%) as well as private hospitals and specialist clinics (1.5%). Doctors (87.2%) contributed the highest number of reports, followed by research coordinators (4.9%) and pharmacists (4.6%). Reports from dentists and nurses have also been received.

**3,177 COVID 19 VAEs were not included as they were reviewed separately. The analysis of COVID-19 VAEs is available on pages 5 - 6.*

(b) Demographics

Majority of the patients in the AE reports were Chinese (38.6%), followed by Malays (6.2%) and Indians (3.5%). The rest were Caucasians (0.1%), Eurasians (0.3%) and patients whose ethnicity were unreported (51.2%). More AE reports were received for females (61.3%) than males (37.6%). The age of the patients ranged from 0 days old to 106 years old, with most reports comprising elderly patients in the age group of 60 to 69 years old (15.6%) followed by patients in the age group of 50 to 59 years old (14.5%). In 9.6% of the reports, the patient's age was unspecified.

Adverse event reports associated with drugs, biologics and CTGTP

The top 20 products suspected of causing AEs were from the following pharmacotherapeutic groups: nonsteroidal anti-inflammatory agents (NSAIDs) (19.3%), antibiotics (17.7%), analgesics (10.4%), drugs for cardiovascular system (CVS) (5.3%), gastrointestinal agents (2.8%) and contrast media (2.7%) (Figure 1). It is worth noting that these figures do not take into consideration the products' utilisation rates and therefore do not inform on their relative safety profiles.

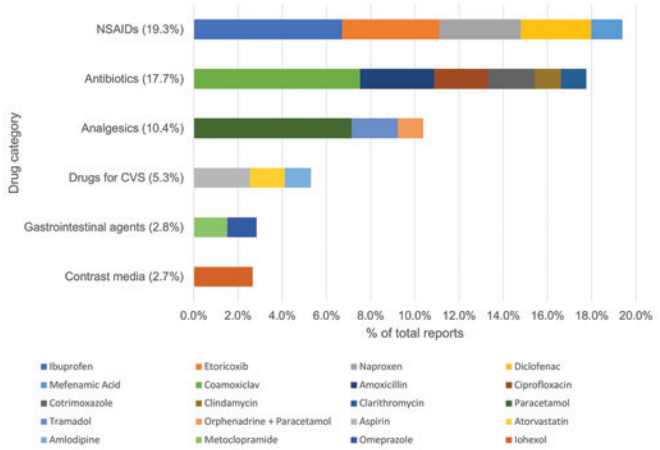

Figure 1. Top 20 products (by active ingredients) suspected of causing AEs

A large proportion of AEs reported were associated with skin reactions (60.4%), followed by those affecting the body as a whole (e.g., fever, anaphylaxis) (20.5%) and respiratory system disorders (6.5%). Most AE reports described non-serious reactions (e.g., rash, periorbital oedema, nausea, and vomiting). Table 1 summarises selected serious AEs and the suspected products.

Vaccine adverse event reports

HSA received 236 VAE reports in 2022, excluding those associated with COVID-19 vaccines. Of these, 86 (36.4%) reports involved adults and 142 (60.2%) reports involved paediatrics below the age of 18. Age was not reported in the remaining 8 (3.4%) reports. Most of the reports in children aged 12 years and below were from the active surveillance site at KK Women's and Children's Hospital (n=120, 50.8%), which HSA partners to screen paediatric hospital admission for AEs post-vaccination.

The most commonly reported VAE in children aged 12 and below was lymphadenopathy with the Bacillus Calmette-Guerin (BCG) vaccine. Other commonly reported AEs in this age group included seizures (febrile and afebrile), Kawasaki disease, rashes and injection site reactions associated with various types of vaccines. Seizures were most frequently reported with measles, mumps, and rubella (MMR) vaccine (n=11); measles, mumps, rubella, and varicella (MMRV) vaccine (n=5) and pneumococcal conjugate vaccine (n=8). Other serious AE reports included meningitis and thrombocytopenia with various vaccines. There were also isolated reports of appendicitis with human papillomavirus (HPV) vaccine as well as Gianotti-Crosti syndrome˘ and joint pain with Tdap*-inactivated polio and influenza vaccines. AEs in children above 12 years include fever, seizures and thrombocytopenia with HPV vaccine and an isolated report of appendicitis associated with Tdap* and inactivated polio vaccine.

The most commonly reported AEs in adults were allergic reactions such as rash, angioedema and injection site reactions with vaccines, including seasonal influenza, hepatitis B, pneumococcal, tetanus, HPV, and MMR vaccines. Serious AE reports included anaphylaxis with various vaccines and isolated reports of acute generalised exanthematous pustulosis with measles vaccine and systemic inflammatory response syndrome with pneumococcal conjugate vaccine.

HSA's review of the VAE reports in 2022 did not identify any new safety concerns. Overall, the VAEs received in 2022 were within the expected AE frequencies listed in the vaccine package inserts or in literature.

**Tdap refers to Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine*

˘Gianotti-Crosti syndrome (also known as papular acrodermatitis of childhood) is a benign, self-limiting disease characterised by an acute eruption of monomorphic skin-coloured to pink-red papules on the face, buttocks, and extensor surfaces of the extremities.[1]

Table 1. Chemical drugs, biologics and CTGTPs suspected of causing serious AEs

Description	WHO preferred terms	Suspected active ingredient(s) (Number in bracket denotes the number of times the pharmaceutical has been implicated in 2022#)	Top 10 suspected active ingredient(s) from 2018- 2022 (Number in bracket denotes the cumulative number of times the pharmaceutical has been implicated from 2018 to 2022^)
Skin disorders	Acute generalised exanthematous pustulosis (AGEP), Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)	Allopurinol (12), Ampicillin (2), Atorvastatin (2), Azathioprine (2), Cefalexin (5), Cefazolin (8), Ciprofloxacin (6), Clindamycin (3), Coamoxiclav (23), Cotrimoxazole (6), Diclofenac (2), Esomeprazole (2), Ethambutol (2), Etoricoxib (3), Hydroxychloroquine (2), Iohexol (2), Levofloxacin (2), Meropenem (3), Omeprazole (14), Paracetamol (2), Pembrolizumab (5), Phenytoin (2), Piperacillin and Tazobactam (17), Rifampicin (2), Tramadol (3), Vancomycin (4)	Allopurinol (63), Cefazolin (21), Clindamycin (23), Coamoxiclav (79), Cotrimoxazole (37), Etoricoxib (18), Meropenem (18), Omeprazole (54), Piperacillin and Tazobactam (54), Vancomycin (23)
Body as a whole	Anaphylactic Reaction	Acetylcysteine (2), Alteplase (2), Amoxicillin (8), Aspirin (8), Atracurium (13), Benzylpenicillin or Penicillin G (5), Bupivacaine (2), Cefalexin (3), Cefazolin (13), Celecoxib (3), Chlorhexidine (6), Ciprofloxacin (4), Clarithromycin (2), Coamoxiclav (21), Codeine (2), Dexamethasone (2), Diclofenac (13), Etoricoxib (2), Fentanyl (5), Ferric Carboxymaltose (2), Fluorescein (3), Ibuprofen (12), Iodixanol (2), Iohexol (7), Lidocaine (7), Loratadine (2), Macrogol (2), Mefenamic Acid (3), Metoclopramide (2), Metronidazole (6), Naproxen (9), Omeprazole (4), Ondansetron (2), Orphenadrine and Paracetamol (2), Paclitaxel (5), Paracetamol (15), Piperacillin and Tazobactam (8), Propofol (4), Pseudoephedrine (2), Suxamethonium or Succinylcholine (2), Tramadol (2)	Amoxicillin (27), Atracurium (39), Cefazolin (51), Coamoxiclav (84), Diclofenac (67), Ibuprofen (56), Iohexol (38), Naproxen (48), Paracetamol (55), Piperacillin and Tazobactam (34)
Central nervous system disorders	Convulsions, Convulsions Grand Mal, Encephalopathy, Meningoencephalitis, Neuroleptic Malignant Syndrome, Neurologic toxicity	Aciclovir (2), Ertapenem (3)	Atezolizumab (4), Cefepime (7), Ertapenem (15), Flupenthixol (3), Gabapentin (3), Haloperidol (8), Ketamine (3), Levetiracetam (3), Metoclopramide (6), Tisagenlecleucel (4)
Renal disorders	Azotaemia, Creatinine Clearance Decreased, Glomerulonephritis, Interstitial Nephritis, Nephrosis, Renal Failure Acute/Chronic, Renal Function Abnormal, Renal Tubular Disorder/Necrosis, Toxic Nephropathy	Aciclovir (2), Ciprofloxacin (8), Clarithromycin (2), Cotrimoxazole (2), Enalapril (4), Etoricoxib (5), Hydrochlorothiazide (2), Ibuprofen (3), Lisinopril (2), Losartan (4), Metformin (2), Telmisartan (3)	Ciprofloxacin (56), Cotrimoxazole (12), Diclofenac (18), Enalapril (20), Etoricoxib (23), Hydrochlorothiazide (9), Ibuprofen (23), Lisinopril (19), Losartan (38)
Hepatic disorders	Hepatic Coma, Hepatic Cirrhosis, Hepatic Failure, Hepatitis, Hepatitis Cholestatic, Hepatic Enzymes Increased, Hepatic Failure, Hepatocellular Damage, Liver Injury	Abemaciclib (2), Allopurinol (4), Amiodarone (2), Amlodipine (2), Amoxicillin (2), Atorvastatin (19), Azathioprine (3), Ciprofloxacin (3), Coamoxiclav (6), Cotrimoxazole (3), Fenofibrate (3), Gabapentin (2), Isoniazid (2), Piperacillin and Tazobactam (2), Rifampicin (3), Sulfasalazine (3), Valproate (3)	Allopurinol (23), Atorvastatin (122), Azathioprine (30), Coamoxiclav (53), Cotrimoxazole (31), Fenofibrate (18), Fimasartan (13), Methotrexate (13), Simvastatin (17), Sulfasalazine (15)

\# *More than one suspected product may be implicated in a single AE report. Only active ingredients reported more than once are listed here*
^ *Based on onset date of the AE*

Complementary health products adverse event reports

There were 71 AE reports involving CHPs, of which 47 (66.2%) implicated products classified as health supplements. Majority of these were associated with glucosamine-containing products (n=25, 53.1%) describing mostly hypersensitivity reactions (rash and pruritus). HSA received five reports of allergic reactions with probiotic products, of which two were anaphylaxis reports. The probiotic products were subsequently found to contain cow's milk protein which triggered the allergic reactions in patients with pre-existing milk/food allergies. HSA had published an 'AE case in focus' article in the Dec 2022 issue of the bulletin for one of these anaphylaxis reports.[2] Other CHP AE reports included two reports of raised liver enzymes with Hemohim (a product with claims for immune support). There were five AE reports associated with adulterated products ('Flash Slim', 'Star Cream', 'Tao Ju Hui Yi Mei Li Shang Kou Hu Li Ruan Gao', 'AlphaMiracHERBS' and 'Shu Jin' capsules). Products containing undeclared steroids led to Cushing's syndrome, adrenal insufficiency and/or osteoporosis in several patients. Press releases were issued to alert the public of these products.[3]

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3. https://www.hsa.gov.sg/announcements?contenttype=press%20releases

Analysis of COVID-19 vaccine adverse event reports for year 2022

Key Points

- HSA received 3,177 COVID-19 vaccine adverse event (AE) reports in 2022
- Majority of the reported AEs were non-serious reactions. Serious AEs reported include serious allergic reactions, myocarditis, pericarditis and persisting symptoms such as dyspnoea, tachycardia and urticaria
- HSA is closely monitoring the AEs with COVID-19 vaccines and assesses them in the context of their background incidence rates and patients' underlying medical conditions. Overall, the benefits of the COVID-19 vaccines continues to outweigh the known risks

This is a review of the COVID-19 vaccine adverse event (AE) reports received by HSA from healthcare professionals for 2022. A total of 3,177 COVID-19 vaccine AE reports were received, which were lower than the number of reports received in 2021 i.e., 15,035 reports.

The COVID-19 vaccines used in Singapore are:
- Monovalent and Bivalent mRNA vaccines: Pfizer-BioNTech Comirnaty, Moderna/Spikevax
- Protein subunit vaccine: Nuvaxovid
- Inactivated vaccines: Sinovac-CoronaVac, Sinopharm

Monovalent mRNA vaccines accounted for the majority of the vaccines administered in Singapore. They comprised 80.3% (4,253,592 doses) of the total doses administered, followed by the Bivalent Original/Omicron mRNA vaccines* (12.9%), inactivated COVID-19 vaccines (5.9%) and Nuvaxovid COVID-19 vaccine (0.8%).

**Moderna/Spikevax Bivalent Original/Omicron COVID-19 vaccine was authorised by HSA as a booster vaccine for individuals aged 18 years and above and Pfizer-BioNTech/Comirnaty Bivalent Original/Omicron COVID-19 vaccine was authorised as a booster vaccine for individuals aged 12 years and above under PSAR on 14 September 2022 and 11 October 2022 respectively.*

AEs with Monovalent mRNA COVID-19 Vaccines

HSA received 2,950 AE reports (reporting rate of 0.07%) for monovalent mRNA COVID-19 vaccines in 2022, of which most were with Pfizer-BioNTech/Comirnaty vaccine (86%). One thousand nine hundred and eighty-four reports (67.2%) involved individuals aged 12 years and above, 830 reports (28.1%) involved children aged 5 to 11 years, and 8 reports (0.3%) involved children aged 4 years and below. The remaining reports were of unknown age as the data was not reported.

Majority of the AEs were non-serious reactions including urticaria, angioedema and rash. Three hundred and twenty-eight reports were assessed as serious (11.1%), which included anaphylaxis and serious allergic reactions, myocarditis, pericarditis, seizures, exacerbation of underlying renal conditions, thrombocytopenia, autoimmune conditions, appendicitis, and events describing persisting symptoms of dyspnoea, reduced effort tolerance, tachycardia or urticaria. The serious AE reporting rates for the first and second booster doses were at 0.005% (119 reports) and 0.001% (9 reports), respectively, which were lower compared to the primary doses at 0.017% (200 reports) in 2022.

The AE reporting rate for booster doses of Pfizer-BioNTech/Comirnaty vaccine in children aged 5 to 11 years[+] was 0.03% (26 reports), which was lower than the AE reporting rate for the primary vaccination series in this age group (0.15%). These AEs were mostly non-serious and these included fever, headache, musculoskeletal chest pain, palpitations, joint pain, rash, and vomiting. There were two serious AEs, one describing myocarditis and the other was thrombocytopenia.

The AE reporting rate of Moderna/Spikevax vaccine in children aged 4 years and below[+] was 0.05% (8 reports). There were five serious reports which included febrile seizures, Kawasaki disease, fever, and vomiting. Febrile seizures and Kawasaki disease are rare events that have been reported following childhood vaccination and can be associated with childhood illnesses.

[+]Monovalent Pfizer-BioNTech/Comirnaty vaccine was rolled out as booster doses to children aged 5 to 11 years on 25 October 2022. Monovalent Moderna/Spikevax vaccine was rolled out as primary vaccination to children aged 6 months to 4 years on 25 October 2022.

AEs with Bivalent Original/Omicron mRNA COVID-19 Vaccines

HSA received 59 and 11 AE reports (reporting rate of 0.012% and 0.005%) for Moderna/Spikevax Bivalent Original/Omicron COVID-19 vaccine and Pfizer-BioNTech/Comirnaty Bivalent Original/Omicron COVID-19 vaccine^ respectively.

The AEs reported for the bivalent mRNA vaccines were similar to those reported for the monovalent vaccines, describing mostly non-serious AEs such as allergic reactions, which included rash/urticaria, angioedema, fever, giddiness, chest pain, syncope and elevated blood pressure. There were six serious AEs reported for Moderna/Spikevax Bivalent vaccine and two serious AEs for Pfizer-BioNTech/Comirnaty Bivalent vaccine. These reports included serious allergic reactions, anaphylaxis, myocarditis, hypotension with tachycardia and hearing loss. The serious AE reporting rates for the two vaccines were similar, at 0.001%, which was lower compared to the monovalent vaccines (0.008%) in 2022.

^Moderna/Spikevax and Pfizer-BioNTech/Comirnaty Bivalent Original/Omicron COVID-19 vaccine were rolled out on 14 October 2022 and 12 December 2022 respectively.

AEs with Nuvaxovid, Sinovac-CoronaVac, and Sinopharm COVID-19 Vaccines

HSA received 40 AE reports (reporting rate of 0.1%) for Nuvaxovid COVID-19 vaccine[#], 96 AE reports (reporting rate of 0.04%) for Sinovac-Coronavac and 25 AE reports (reporting rate of 0.04%) for Sinopharm COVID-19 vaccines in 2022. The number of reports received for these non-mRNA COVID-19 vaccines corresponded with their fewer number of doses administered to the population (355,473 doses of the non-mRNA vaccines compared to 4,938,640 of the mRNA vaccines).

Majority of the reports were non-serious reactions, describing allergic reactions such as angioedema and rash/urticaria, dyspnoea and dizziness. There were 23 serious AEs which included 14 serious allergic reactions (ten were anaphylaxis reactions). These serious allergic reactions were reported with Nuvaxovid and Sinovac-CoronaVac COVID-19 vaccines and occurred in susceptible individuals who had prior reactions to other COVID-19 vaccines and/or history of multiple drug allergies. Other serious AEs reported included events of tachycardia, neuropathy, myopericarditis, hearing loss, persistent urticaria and atopic dermatitis.

[#]Nuvaxovid COVID-19 vaccine was rolled out on 18 May 2022.

HSA is closely monitoring the AEs with COVID-19 vaccines and assessing them in the context of their background incidence rates and patients' underlying medical conditions. Overall, the benefits of the COVID-19 vaccines continue to outweigh the known risks.

High-dose vitamin B6 and risk of peripheral neuropathy

Key Points

- Peripheral neuropathy is a known safety concern that has been associated with chronic high-dose (>100mg/day) vitamin B6, although the precise dose-response relationship and duration threshold have not been clearly established
- Healthcare professionals may consider reviewing the dose and duration of vitamin B6 intake (including over-the-counter health supplements) by patients who present with symptoms of peripheral neuropathy

Vitamin B6 is a water-soluble vitamin that comprises different related compounds (vitamers) such as pyridoxine, pyridoxal, pyridoxamine and pyridoxal 5'-phosphate (PLP). The majority of vitamin B6 supplements contain the biologically inactive form, pyridoxine, which is converted by the body into the biologically active form, PLP. PLP functions as an important co-enzyme in various metabolic processes and neurotransmitter synthesis.[1]

Locally, vitamin B6 is present in both health supplements and therapeutic products, with the latter generally indicated for vitamin deficiency prevention, and treatment of nerve pain and neuropathies. The maximum allowable daily limit for vitamin B6 in health supplements is 100mg/day based on data from several long-term studies.[2,3] This limit is aligned with the upper limit set by ASEAN, Canada and the US for vitamin B6.

Peripheral neuropathy has been reported following chronic high-dose (>100mg/day) consumption of vitamin B6. Healthcare professionals may consider reviewing the dose and duration of vitamin B6 intake (including over-the-counter health supplements) by patients who present with symptoms of peripheral neuropathy.

Vitamin B6-induced peripheral neuropathy

While peripheral neuropathy is a known safety concern with vitamin B6, the exact mechanism of this adverse event has not been fully elucidated. Postulated mechanisms include the saturation of enzymes leading to accumulation of free pyridoxine and subsequent neurotoxicity, aldehyde toxicity through elevated PLP concentration, the formation of reactive intermediates and competitive inhibition of PLP-dependent enzymes.[1,4]

The precise-dose response relationship of vitamin B6 causing peripheral neuropathy and the threshold for duration of use have also not been clearly established. Evidence from literature on vitamin B6-related neuropathy is largely based on case reports, case series and small clinical studies, where the vitamin B6 dosage and duration of use ranged from <50mg to >10g, and three days to ten years, respectively.[5] However, limitations were noted in some studies, such as the absence of a physician's assessment or clinical neurological assessment, and potential confounding by the patient's susceptibility to develop neuropathies (e.g., drug, alcohol and nutritional status).

Local situation

To date, HSA has received one local adverse event report in 2020 regarding non-serious severe neuralgia in a 65-year-old Chinese male who took a vitamin B6-containing product. There were no further details on the dose and duration of vitamin B6 consumption in the report. The local package inserts of therapeutic products that provide a vitamin B6 daily dose exceeding 100mg are in the process of being strengthened to include warnings on peripheral neuropathy.

HSA's advisory

While the effect of peripheral neuropathy usually occurs when vitamin B6 is consumed in high doses and/or over long duration, the mechanism of the adverse event, precise dose-response relationship, and threshold for duration of use have not been clearly established. Healthcare professionals may consider reviewing the dose and duration of vitamin B6 intake (including over-the-counter health supplements) by patients who present with symptoms of peripheral neuropathy.

References

1. *PharmaNutrition 2020; 12: 100188*
2. *https://www.hsa.gov.sg/health-supplements/overview*
3. *National Academies Press 1998: 150-195*
4. *Adv Nutri. 2021; 12: 1911-29*
5. *Drug Saf 2018; 41: 859-69*

Navigation made easy – explore HSA's website for adverse event reporting and safety information related to health products

The HSA website is a key communication channel to healthcare professionals. HSA publishes resources on adverse event (AE) reporting and safety communication related to health products such as Dear Healthcare Professional Letters, educational materials, Adverse Drug Reaction (ADR) News Bulletins and safety alerts on the website. This facilitates healthcare professionals' access to regulatory information on safety issues related to health products. As AE reporting by healthcare professionals and industry members forms the cornerstone of HSA's safety monitoring, HSA has put up a Q&A guide to help healthcare professionals locate relevant information on how to report AEs and what type of information constitutes a good AE report.

1. How to report AEs to HSA?

Report AEs online or via the mobile-friendly e-form. Reporting forms may also be downloaded and emailed to HSA_productsafety@hsa.gov.sg. More information can be found here: https://www.hsa.gov.sg/adverse-events.

AEs may also be reported through the Critical Medical Information Store (CMIS), which is accessible via the public healthcare institutions' electronic medical record system.

2. What types of AEs to report and what information to include?

The types of AEs to report are:

- Serious AEs, even if the events are well known. This allows HSA to continually monitor the incidence of the AEs locally and assess if there is a safety concern. Additionally, medicines in the same therapeutic class can be compared to assess their relative safety
- Unexpected AEs such as those not consistent with the product package insert or label
- AEs occurring with the use of new health products i.e., those marketed in Singapore for less than 5 years

The information required are:

- Patient's details
- Reporter's details
- Information about the AE
- Suspected health product
- Concomitant health product
- Medical history of the patient
- Seriousness and outcome of the event
- Treatment of AE

Watch this video guide (https://www.youtube.com/watch?v=4II-UVEe3QU) to know how to report, how to assess AE causality and how reports by healthcare professionals contribute to the safety surveillance of health products in Singapore.

More information can be found here: https://www.hsa.gov.sg/adverse-events/healthcare-professionals'-guide-to-adverse-events-reporting

3. Where to find AE reporting guides?

AE reporting guides on specific AEs are found here: https://www.hsa.gov.sg/adverse-events/healthcare-professionals'-guide-to-adverse-events-reporting. These guides facilitate the identification, monitoring, management and reporting of AEs to HSA. Refer to Figure 1 for the full listing.

Figure 1. A screenshot of the webpage listing all the available AE reporting guides.

4. Where are safety communication related to health products found?

Safety communication such as abstracts of Dear Healthcare Professional Letters (DHCPLs), ADR News Bulletins, safety alerts etc. are published under the 'Announcements' category: https://www.hsa.gov.sg/announcements, and is accessible via HSA's homepage. The full list of announcements can be found under 'Content type' on the webpage (Refer to Figure 2). Details of the DHCPLs can be found on the MOH Alert System, which is accessible via the Health Professionals Portal (HPP) at https://www.moh.gov.sg/hpp/

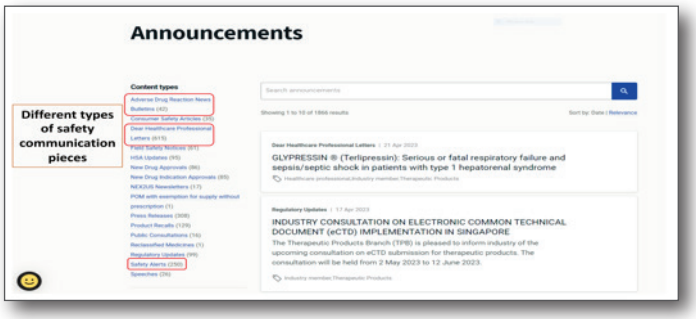

Figure 2. Different types of safety communication pieces categorised based on its 'Content types'

Tip!
To look for a specific communication piece, use the 'filters' found on the webpage. These filters can be applied based on '**Content types**', '**Audience**', '**Product types**' and '**Date published**'. See Figure 3 for an example on the use of 'filters'.

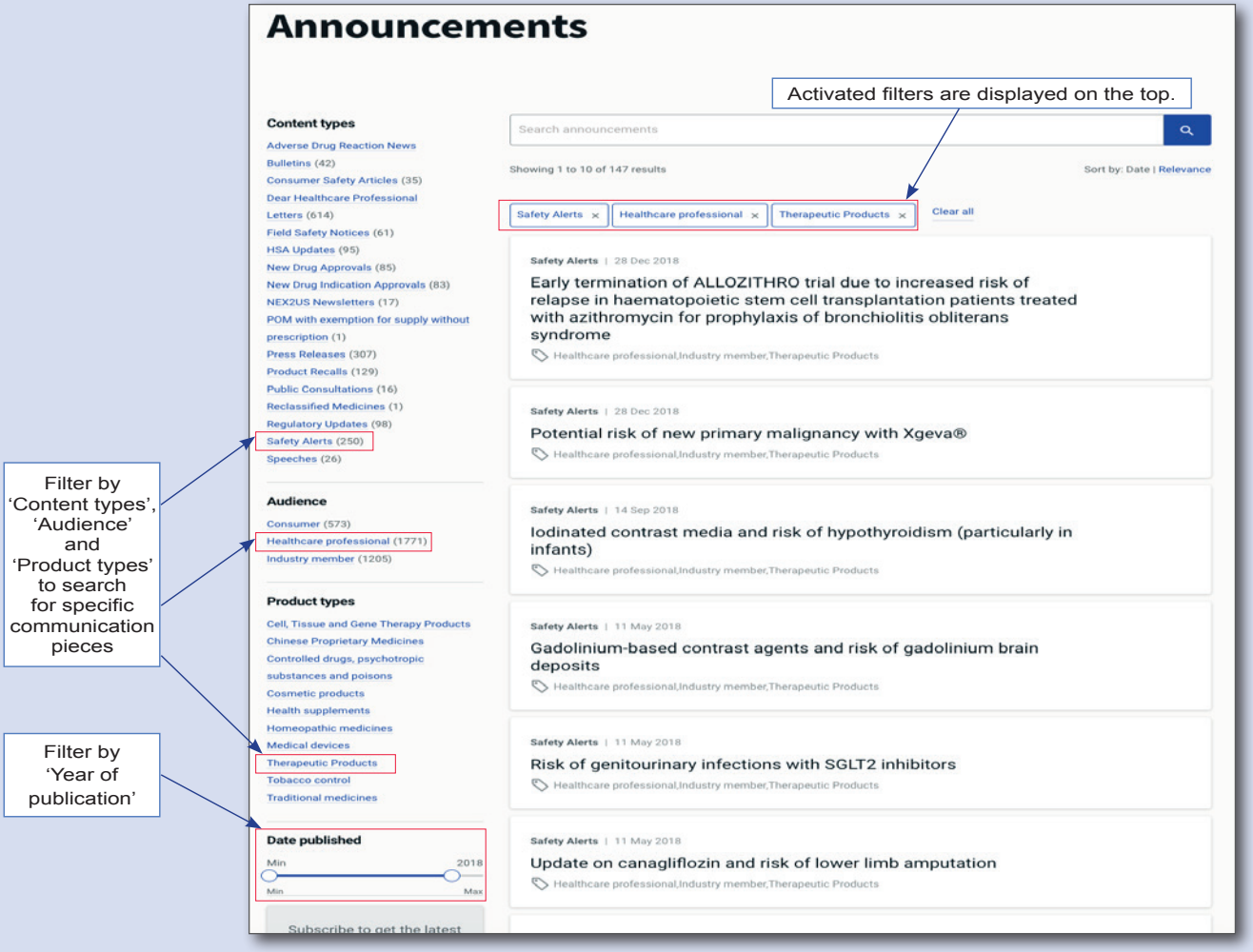

Figure 3. An example on the use of filters to look for 'Safety Alerts' communication related to 'Therapeutic products' targeted at 'Healthcare professionals' and published in the period up to 2018.

5. *Where are educational materials for healthcare professionals found and what is their purpose?*

HSA-approved educational materials for healthcare professionals can be found here: https://www.hsa.gov.sg/educational-materials-for-HCP. They are developed for selected therapeutic products and cell, tissue or gene therapy products (CTGTP) to highlight specific safety concerns and provide advice to optimise their safe and effective use. These materials can be targeted at physicians and healthcare professionals (i.e., Physician Educational Material), or directed at patients (i.e., Patient Medication Guide and Patient Alert Card). Healthcare professionals are encouraged to utilise these educational resources to support clinical decisions and as an aid in counselling patients.

Tip!
To find the educational material(s) for the product of interest, key in the active ingredient or brand name into the Search box (Figure 4).

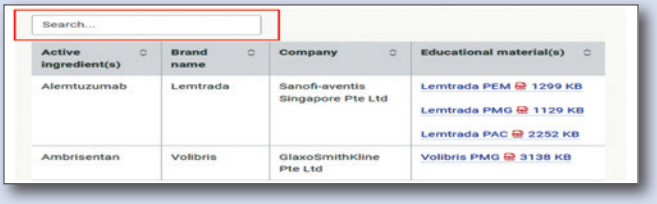

Figure 4. The 'Search' function for educational materials on the webpage

Conclusion

Subscribing to HSA's website at (https://www.hsa.gov.sg/subscribe) will help healthcare professionals stay up to date on safety issues related to health products.

Please send your enquiries, comments and suggestions to:

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