ISSN: 0219 - 2152 Sep 2022 Vol.24 No.2

# ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

## Health Product Safety Information Summary

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



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

## AE Case in Focus: Test Yourself

**What could have caused the Stevens-Johnson syndrome / toxic epidermal necrolysis?** Pg 4

An 80-year-old female was started on acalabrutinib 100 mg twice a day as monotherapy for chemo-refractory diffuse large B-cell lymphoma (DLBCL). Her past medical history included hypertension, hyperlipidaemia, type 2 diabetes mellitus, chronic microvascular infarcts, previous right hip fracture, adrenal insufficiency and gastric ulcers. Apart from acalabrutinib, she was also on aciclovir, co-trimoxazole, amlodipine, calcitriol, calcium carbonate, colecalciferol, denosumab, hydrocortisone and melatonin.

On Day 44 of her treatment with acalabrutinib, she was admitted to the hospital with generalised exanthem, lip and face swelling and conjunctivitis. Two days after admission, her rash morphology evolved into atypical target lesions with positive Nikolsky sign. A skin biopsy showed interface dermatitis with epidermal necrosis, compatible with Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN). The body surface area covered with erythema/purpura was about 25% (Figure 1). There were also erosions noted on her vulva.

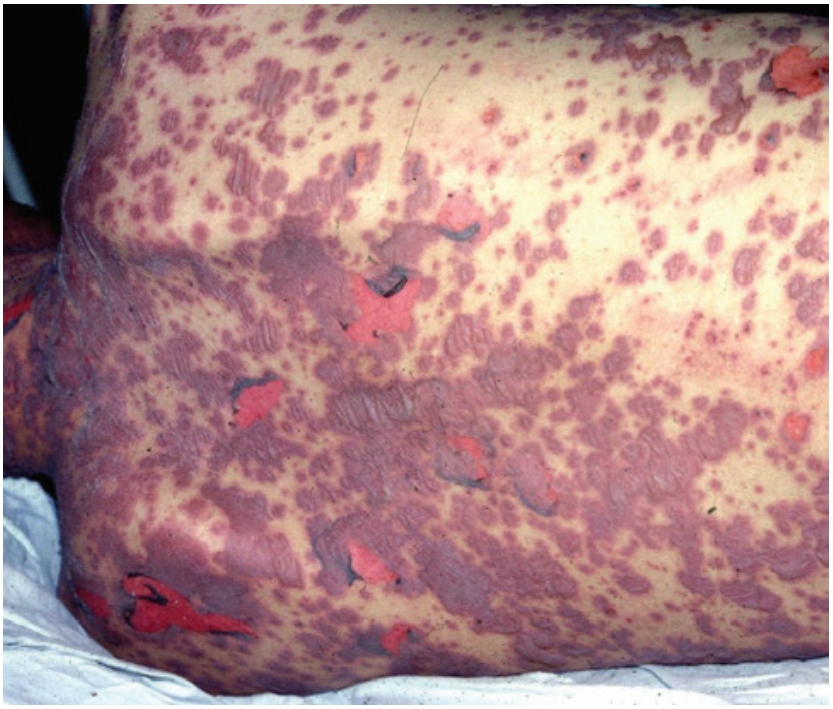

Figure 1. Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN)

## Singapore Food Agency's advisory on the potential risk of bronchiolitis obliterans with the consumption of a raw vegetable

HSA would like to inform healthcare professionals on the recent publication by the Singapore Food Agency (SFA) on the potential risk of bronchiolitis obliterans with the consumption of large amounts of raw or not thoroughly cooked leafy vegetable *Sauropus androgynus* (also known as Cekur Manis, Ma Ni Cai (马尼菜), Sabah vegetable, Star Gooseberry, Katuk and Sweet Leaf). It is a popular leafy vegetable native to Southeast Asia and is often eaten boiled or stir-fried.

https://www.sfa.gov.sg/food-information/risk-at-a-glance/cekur-manis

Bronchiolitis obliterans is a serious and permanent medical condition of the lung where the bronchioles are blocked by inflamed scar tissue, causing irreversible breathing difficulties that can worsen with time and lead to death.

Healthcare professionals are encouraged to report suspected cases of bronchiolitis obliterans associated with the consumption of uncooked *Sauropus androgynus* to SFA at https://csp.sfa.gov.sg/feedback.

## Dear Healthcare Professional Letters on safety concerns


## 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 2022.

# SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) AND RISK OF SUICIDALITY

## Key Points

- SSRIs are known to be associated with an age-dependent risk of suicidality, where an increased risk is observed particularly in patients below 25 years of age, although the causal association remains to be established
- From 2017 to 2021, HSA noted an increasing trend in the prescriptions of SSRIs locally
- When considering the use of SSRIs for patients, healthcare professionals are reminded to be aware of this age-dependent risk of suicidality, particularly in patients aged below 25 years
- Healthcare professionals are also encouraged to refer to the available Medication Information Leaflets (MILs) on SSRIs during medication counselling to their patients and/or caregivers. This is to facilitate the communication of SSRI use and their side effects

Selective serotonin reuptake inhibitors (SSRIs) are used for the treatment of depression, anxiety and other mood disorders. The locally registered SSRIs include escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. They are mostly indicated for patients aged 18 years and above. Fluvoxamine is approved for use in children aged 8 years and above for the treatment of obsessive-compulsive disorder (OCD). Although none of the registered SSRIs are approved specifically for the treatment of depression in children and adolescents below 18 years old, they are used off-label in this patient population. Depression and other psychiatric disorders in children and adolescents can have significant consequences if not appropriately treated. The off-label use of SSRIs is supported by clinical guidelines.[1, 2]

## SSRI-associated suicidality

SSRIs are known to be associated with an age-dependent risk of suicidality, where an increased risk is observed particularly in patients less than 25 years of age. However, the causal association remains to be conclusively established, as the risk of suicidality may be confounded by the patient's underlying psychiatric condition and its severity. A meta-analysis of 24 short-term placebo-controlled trials of major depressive disorder (MDD) or other psychiatric disorders involving over 4,400 children and adolescents found a greater risk of suicidal ideation and behaviour (but not completed suicide) during the first few weeks after treatment initiation with SSRIs as compared with placebo (4% vs 2%; risk ratio 1.95, 95% confidence interval [CI] 1.28 to 2.98).[3] Similarly, another pooled analysis of 295 short-term (median duration 2 months) placebo-controlled trials of 11 antidepressant drugs, of which the majority were SSRIs, in over 77,000 adults with MDD or other psychiatric disorders found a higher risk of suicidal behaviour associated with antidepressant use among patients less than 25 years old (odds ratio [OR] 2.30, 95% CI 1.04 to 5.09).[4] However, no increased risk was observed in adults aged 25 to 64 years (OR 1.03, 95% CI 0.68-1.58) and a risk reduction was observed in adults aged 65 years old or greater (OR 0.06, 95% CI 0.01-0.58).

## Local prescribing trends of SSRIs

Based on data from the electronic medical records, an average of 50,000 patients were prescribed SSRIs annually between 2017 and 2021. Of these patients, the majority were adults (≥25 years of age; 82.9%), followed by young adults (18-24 years; 13.5%) and children/adolescents (<18 years; 3.6%).

Over those five years, an increasing trend in the prescriptions of SSRIs was observed. The increase ranged from 3.5% to 4.7% year-on-year from 2017 to 2020, followed by a bigger jump of 9.1% from 2020 to 2021. When analysed by age group, the annual proportion of children or adolescents prescribed SSRIs was stable at around 3.4% from 2017 to 2020 and increased to 4.1% in 2021, while those of young adults steadily increased over the years from 11.2% in 2017 to 15.5% in 2021 (Figure 1). In contrast, there was a downward trend in the annual proportion of adults prescribed SSRIs from 85.4% in 2017 to 80.5% in 2021.

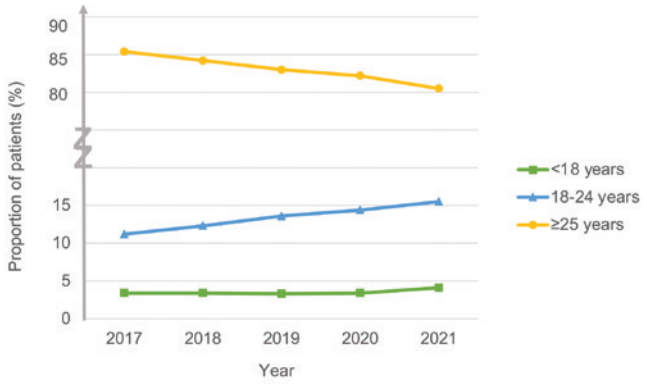


*Figure 1. Trend in proportion of patients prescribed SSRIs by age group*

## Local educational materials for patients

Patient educational materials on SSRIs are available on publicly accessible platforms, including the Medication Information Leaflets (MILs) on HealthHub.[5] These MILs, which were developed by the National Medication Information Workgroup* with consensus from the College of Psychiatrists as well as the relevant chapter specialties of the College of Physicians, provide a brief overview on the uses of SSRIs and their side effects. The warnings on suicidality and mental state worsening in these MILs have recently been strengthened to highlight such risks in young people aged below 25 years and to improve patient awareness and education.

## HSA's assessment and advisory

HSA, in consultation with its Product Vigilance Advisory Committee, has assessed that while warnings and advisories pertaining to suicidality risk have been highlighted in the local package inserts of SSRIs and patient educational materials, it would be relevant to remind healthcare professionals of SSRI-associated suicidality in young adults and the availability of MILs to aid patient counselling. This is in view of the increase in the use of SSRIs locally.

Healthcare professionals are encouraged to refer to the available MILs on SSRIs during medication counselling to their patients and/or caregivers. This is to facilitate the communication of SSRI use and their side effects.

**This workgroup comprises cluster partners (National Healthcare Group, National University Health System and SingHealth), community pharmacies (Guardian, Unity and Watsons) and the Pharmaceutical Society of Singapore*

### References

1. https://www.ranzcp.org/files/resources/college_statements/practice_guidelines/clinical_guidance_on_the_use_of_antidepressant_med.aspx
2. https://www.nice.org.uk/guidance/ng134
3. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/suicidality-children-and-adolescents-being-treated-antidepressant-medications
4. BMJ. 2009;339:b2880
5. https://www.healthhub.sg/a-z/a?cat=medications

## AE CASE IN FOCUS: TEST YOURSELF

An 80-year-old female was started on acalabrutinib 100 mg twice a day as monotherapy for chemo-refractory diffuse large B-cell lymphoma (DLBCL). Despite her previous treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) followed by R-GemOx (rituximab, gemcitabine and oxaliplatin), her disease showed rapid progression both clinically and on positron emission tomography-computed tomography (PET-CT) scan. She was switched to acalabrutinib in view of her non-germinal centre subtype DLBCL. Her past medical history included hypertension, hyperlipidaemia, type 2 diabetes mellitus, chronic microvascular infarcts, previous right hip fracture, adrenal insufficiency and gastric ulcers. Apart from acalabrutinib, she was also on aciclovir, co-trimoxazole, amlodipine, calcitriol, calcium carbonate, colecalciferol, denosumab, hydrocortisone and melatonin.

Her DLBCL responded to acalabrutinib and the dose was reduced to 100 mg once daily at her follow-up consultation one month after initiation due to her complaint of fatigue. At that time, her skin examination was unremarkable.

On Day 44 of her treatment with acalabrutinib, she was admitted to the hospital with generalised exanthem, lip and face swelling and conjunctivitis. A positron emission tomography (PET) scan was done and the skin lesions were not as fluorodeoxyglucose (FDG)-avid as the rest of her prior DLBCL lesions, raising suspicion of a drug reaction. Two days after admission, her rash morphology evolved into atypical target lesions with positive Nikolsky sign. A skin biopsy showed interface dermatitis with epidermal necrosis, compatible with Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN). The body surface area covered with erythema/purpura was about 25%. There were also erosions noted on her vulva.

### Question: What could have caused the SJS/TEN?

*HSA would like to thank Dr Hwang Kai Wen, Resident, Department of Internal Medicine, National University Health System and Dr Anand D. Jeyasekharan, Department of Haematology-Oncology, National University Cancer Institute, for their contributions to this article.*

## ANSWER TO AE CASE IN FOCUS: TEST YOURSELF

Acalabrutinib was assessed to be the likely culprit for the SJS/TEN (Figure 1) given that the latency period was within what is generally expected i.e., 4 days to 8 weeks and it being the only new drug added to the patient's medication regimen apart from melatonin.[1] Acalabrutinib was promptly discontinued and the patient was treated with oral ciclosporin, analgesics, steroid-containing and lubricating eye drops. She was also transferred to the intensive care unit for close monitoring. However, she subsequently developed multiple infections, leading to septic shock and her eventual demise.

### Dermatologic toxicities with Bruton's tyrosine kinase (BTK) inhibitors

Acalabrutinib (Calquence®, AstraZeneca Singapore Pte Ltd) is a 2nd generation selective, irreversible inhibitor of BTK. It was approved by HSA in July 2019 for the indications of:

- Combination therapy with obinutuzumab or monotherapy for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL) / small lymphocytic lymphoma (SLL),
- Monotherapy for the treatment of patients with CLL/SLL who have received at least one prior therapy, and
- Treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.[2]

BTK is a key component of the B-cell receptor signalling pathway that is responsible for the proliferation, survival and homing of malignant B-cells.[3] BTK inhibitors are indicated for use in B-cell malignancies, including MCL, CLL/SLL, marginal zone lymphoma (MZL), follicular lymphoma and Waldenström macroglobulinaemia. BTK inhibitors also show good clinical activity in relapsed non-germinal centre subtype DLBCL, with ongoing phase III trials evaluating their use. Inhibition of BTK results in diminished proliferation, decreased survival and impaired adhesion and migration of the malignant B-cells to the lymphoid microenvironment. Other locally registered agents in this drug class include ibrutinib (Imbruvica®, Johnson & Johnson Pte Ltd) and zanubrutinib (Brukinsa™, BeiGene Singapore Pte Ltd).

Ibrutinib is the first-in-class inhibitor of BTK. Dermatologic adverse events (AEs) with ibrutinib are mostly mild to moderate, transient and easily managed. The incidence is highest during the first year of treatment and declines over time.[4] Bruising and ecchymoses are the most common and most characteristic dermatologic toxicities of ibrutinib, mediated by on-target BTK and off-target TEC kinases which affect the signalling

### 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.

pathways downstream of several specific platelet membrane receptors (e.g., glycoprotein VI and Von Willebrand factor receptor), leading to the dysfunction of platelet aggregation. Ibrutinib-induced hair and nail abnormalities (textural hair changes, brittle nails), folliculitis, rashes and skin infections (e.g., herpes simplex and herpes zoster virus reactivations, *Staphylococcus aureus* superinfection) are also common.[4,5] While there have been reports of SJS, other serious cutaneous adverse reactions (SCARs) such as TEN, drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP) appear to be rare.[4]

There is limited available information on dermatologic toxicities with acalabrutinib and zanubrutinib as these are newer agents. The overall incidence of toxicities with these next-generation BTK inhibitors are expected to be lower as unlike ibrutinib, they bind to BTK more selectively and have minimal off-target inhibition of alternative kinases (epidermal growth factor receptor [EGFR], SRC-family kinases and other kinases of the TEC family).[4] As of 30 June 2022, one overseas case of SJS associated with acalabrutinib and another overseas case of DRESS associated with zanubrutinib have been reported to Vigibase (the World Health Organisation's global safety database for drugs). A literature search further identified a case of TEN which occurred 45 days after initiation of zanubrutinib in a 63-year-old male with MZL.[6] He subsequently passed away with the cause of death indicated as TEN and disease progression. No other reports of SCARs with acalabrutinib and zanubrutinib have been published in literature at the time of writing. A longer observation period will be required to further understand the safety profile of these newer agents.

Locally, the AE case in focus is the first report of SCAR with BTK inhibitors. Besides SCARs, HSA has also received two reports of bruising, as well as isolated reports of cellulitis and xerosis with ibrutinib. HSA has not received any AE reports associated with zanubrutinib as of 30 June 2022. Healthcare professionals are reminded to report any suspected AEs with newly registered drugs to the Vigilance and Compliance Branch of HSA so that we can continually reassess the risk profiles of these agents.

## Dermatologic toxicities with other oral targeted therapies

The myriad of newly developed targeted therapies has broadened the available treatment options for cancers. However, the novel mechanisms of actions of these drugs are accompanied by a unique array of AEs, particularly dermatologic toxicities. These may be hypersensitivity reactions or a result of the particular antineoplastic agent on its effector molecule or receptor, which can result in treatment non-compliance and increased risk of cutaneous infections.[7,8] Notably, dermatologic AEs occur more frequently and have a greater negative impact on the quality of life in patients on targeted therapies as compared to those on non-targeted therapies, including cytotoxic chemotherapies.[7] Nevertheless, SCARs appear to be rare with targeted therapies.[9] Timely and accurate identification and withdrawal of the causative drugs are crucial in the management of SCARs.

An overview of serious cutaneous AEs associated with the use of selected targeted therapies received by HSA as of 30 June 2022 is presented in Table 1 below.

Table 1. Serious cutaneous adverse event (AE) reports with selected oral targeted therapies

| Drug Class | Drug | HSA approval date | Local reports of serious cutaneous AEs (number of reports) | Commonly reported cutaneous AEs in literature[9-11] |
|---|---|---|---|---|
| EGFR inhibitors | 1st generation<br>Gefitinib<br>Erlotinib<br>Lapatinib | Feb 2003<br>Feb 2006<br>Oct 2007 | Blistering rash over face and periorbital region (1), cutaneous toxicity / rash requiring hospitalisation (3), DRESS (1), erythroderma (1), grade 3 erythematous erosions (1), SJS (1) | Acneiform eruptions, mucositis, photosensitivity, xerosis, paronychia and hair abnormalities |
| | 2nd generation<br>Afatinib<br>Neratinib<br>Dacomitinib | Dec 2013<br>Nov 2019<br>June 2020 | Grade 3 acneiform facial rash (1), mucositis/ maculopapular rash/paronychia requiring hospitalisation (1), scalp and thigh abscesses requiring hospitalisation (1) | |
| | 3rd generation<br>Osimertinib | Dec 2016 | Maculopapular rash requiring hospitalisation (1), SJS (1), severe stomatitis (1) | |
| BRAF-MEK inhibitors | Vemurafenib<br>Dabrafenib-Trametinib | Feb 2013<br>Aug 2015/Feb 2017 | Erythematous annular lesions and pityrosporum folliculitis (1), skin reaction and ankle swelling causing difficulty in walking (1) | Maculopapular eruptions, highly pruritic keratosis pilaris-like eruption, photosensitivity, secondary skin malignancies, alopecia, panniculitis, HFSR and xerosis. Cutaneous toxicity is greatly reduced with BRAF-MEK combination therapy compared to BRAF alone |
| BTK inhibitors | 1st generation<br>Ibrutinib | Jul 2015 | Cellulitis (1) | Bruising and ecchymoses, panniculitis, human herpesvirus infections, cellulitis, rash, nail and hair toxicities |
| | 2nd generation<br>Acalabrutinib<br>Zanubrutinib | Jul 2019 | TEN (1) | |

| | | | | |
|---|---|---|---|---|
| **Multikinase inhibitors** | Sorafenib | Aug 2007 | Grade 3 HFSR (2), grade 3 purpuric rash (1), SJS (1), widespread papular rash requiring hospitalisation (1) | Most commonly HFSR, especially with sorafenib and regorafenib. Seborrheic dermatitis-like rash, alopecia, hair depigmentation, hyperkeratosis, splinter haemorrhages, xerosis and stomatitis |
| | Regorafenib | Jun 2013 | Fixed drug eruption requiring hospitalisation (1), HFSR (2 requiring dose interruption, 1 requiring hospitalisation, 4 grade 3), maculopapular rash (1 requiring hospitalisation, 1 grade 3) | |
| | Sunitinib<br>Pazopanib<br>Axitinib<br>Cabozantinib | Apr 2007<br>Sept 2011<br>Mar 2013<br>Jan 2019 | HFSR requiring treatment discontinuation (1), maculopapular rash requiring hospitalisation (2) | |
| **BCR-ABL tyrosine kinase inhibitors** | 1st generation<br>Imatinib | May 2007 | Rash (1 requiring hospitalisation, 1 requiring dose reduction, 1 grade 4), stomatitis requiring treatment interruption (1) | Most commonly maculopapular rashes and facial edema. Pigmentation disorders, alopecia, keratosis pilaris and xerosis |
| | 2nd generation<br>Dasatinib<br>Nilotinib | Sept 2007<br>July 2008 | DRESS (1), generalised vasculitic urticaria requiring hospitalisation (1), widespread maculopapular rash requiring hospitalisation (1) | |
| | 3rd generation<br>Ponatinib | Nov 2018 | None | |
| **PI3K inhibitor** | Alpelisib | March 2020 | Grade 3/4 rash (4), TEN (1) | Maculopapular rash |

*Abbreviations: BTK, Bruton's tyrosine kinase; DRESS, drug reaction with eosinophilia and systemic reactions; EGFR, epidermal growth factor receptor; HFSR, hand-foot skin reaction; MEK, mitogen-activated protein kinase enzyme; PI3K, Phosphatidylinositol 3-kinase; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.*

To date, HSA has received seven reports of SCARs with oral targeted therapies: SJS (n=3), TEN (n=2) and DRESS (n=2). Similar to a 2018 review of SCARs induced by targeted therapies and immunotherapies by Chen *et al*, SCARs were most commonly reported with EGFR inhibitors locally [SJS: gefitinib (n=1), osimertinib (n=1); DRESS: gefitinib (n=1)].[11] One report of SCAR was received for each of these drug classes: PI3K inhibitor (alpelisib), BTK inhibitor (acalabrutinib), multikinase inhibitor (sorafenib) and BCR-ABL tyrosine kinase inhibitor (nilotinib). Two reports listed co-suspects of fulvestrant and megestrol. There were no reports of AGEP received. All the patients were females with a median age of 73 years (range: 61 to 81 years; age was unknown for one case). Information on the time-to-onset was available for four reports and ranged from 12 to 64 days. One patient was reported to have recovered, two patients (one each for SJS and TEN) had fatal outcomes, while outcomes for the remaining four patients were unreported. SJS and TEN are known to be life-threatening skin disorders, with mortality rates of 26.9% for SJS/TEN and 52.4% for TEN reported in the literature review by Chen *et al*.[11] In the same review, imatinib and vemurafenib were among the top three therapies to cause SJS/TEN and imatinib was the most common drug to induce DRESS and AGEP. However, no local reports of SCARs have been received for imatinib and vemurafenib.

Figure 1. Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN)

## Role of healthcare professionals in AE monitoring

There is a wide range of potential dermatologic AEs that may occur with the use of oral targeted therapies. The European Society of Medical Oncology clinical practice guidelines published in 2021 provide some useful recommendations on the management of dermatologic AEs induced by targeted therapies.[12] Healthcare professionals may consider educating their patients to self-monitor for potential dermatologic AEs and to seek prompt medical attention when necessary. Healthcare professionals are encouraged to report any suspected AEs to the Vigilance and Compliance Branch of HSA.

### References


1. *Clin Pharmacol Ther. 2010; 88: 60-8.*
2. *Singapore package insert for Calquence®. Approved 28 May 2020.*
3. *Haematologica. 2017; 102: 1629-39.*
4. *Am J Clin Dermatol. 2020; 21: 799-812.*
5. *JAMA Dermatol. 2016; 152: 698-701.*
6. *Br J Haematol. 2022; 198: 62-72.*
7. *Am J Clin Dermatol. 2013; 14: 327-33.*
8. *J Natl Cancer Inst. 2010; 102: 47-53.*
9. *Int J Womens Dermatol. 2021; 7: 615-24.*
10. *Front Cell Dev Biol. 2021; 9: 630942.*
11. *Cancer Manag Res. 2018; 10: 1259-73.*
12. *Ann Oncol. 2021; 32:157–70.*

# QT PROLONGATION AND TORSADES DE POINTES WITH DONEPEZIL

## Key Points

- Cases of QT prolongation and Torsades de Pointes associated with donepezil have been reported overseas and in the published literature
- The local package inserts for donepezil products are being updated to include warnings on the above safety concerns and their risk factors
- Healthcare professionals are advised to consider these safety concerns when prescribing donepezil to patients with pre-existing or family history of QT prolongation, relevant pre-existing cardiac disease, electrolyte disturbances, or taking concomitant drugs known to affect the QT interval
- Healthcare professionals may wish to consider electrocardiogram (ECG) evaluation as part of the clinical monitoring of at-risk patients

Donepezil is a specific and reversible inhibitor of acetylcholinesterase registered under several brand names in Singapore since 1998. It is indicated for the symptomatic treatment of mild to moderate and severe Alzheimer's dementia. Cases of QT prolongation and Torsades de Pointes (TdP) associated with donepezil have been reported overseas and in published literature.

## About QT prolongation and Torsades de Pointes[1-3]

QT prolongation refers to a delayed interval between the onset of ventricular depolarisation to the end of ventricular repolarisation, which can predispose to arrhythmias. It can either be congenital or acquired, with the latter being more prevalent. Acquired QT prolongation is often drug-induced or a result of structural heart disease such as myocardial infarction and left ventricular hypertrophy.

Excessive QT prolongation could lead to TdP, a potentially life-threatening form of polymorphic ventricular tachycardia that may manifest as palpitations, syncope, seizure-like activity or sudden cardiac arrest. Risk factors for TdP include older age (>65 years), female gender, uncorrected electrolyte imbalances, family history of QT prolongation, pre-existing cardiovascular disease (e.g., heart failure, myocardial infarction, bradycardia), and recent cardioversion with QT-prolonging drugs.

Many drugs associated with QT prolongation and TdP inhibit potassium channels that mediate the cardiac rapid delayed rectifier current ($I_{kr}$), which in turn leads to a prolonged ventricular action potential duration and an extended repolarisation phase. These channels are encoded by KCNH2 or hERG. In preclinical safety evaluation using mammalian expression system, donepezil and its metabolites have been found to inhibit the hERG channel ionic current recorded from hERG channels. In addition to channel inhibition, donepezil also impairs channel trafficking to the cell membrane and decreases mature channel membrane density.

## Findings from recent published literature

Kho *et al*. conducted a single-centre retrospective analysis to investigate the effect of long-term donepezil therapy on electrocardiogram (ECG) changes, in particular its effects on the QT interval.[4] A resting 12-lead ECG obtained during the most recent acute hospital admission was compared to the ECG prior to commencing donepezil therapy. Fifty-nine patients who were on donepezil therapy for at least a year and 53 controls (matched for age, gender, ethnicity and comorbidities) were included in the study.

The study found that long-term use of donepezil (≥1 year) was associated with significantly prolonged QT intervals (393.3 ± 35.6ms at baseline vs 411.9 ± 44.6ms on donepezil; p=0.002), and the results remained consistent across the QT corrected using Bazett (QTcB), Fredericia, Framingham and Hodges formulae. Among those treated with donepezil, 16 male and 11 female patients presented with QT prolongation, defined in the study as QTcB interval ≥450ms and ≥460ms respectively, with the longest QTcB interval at 570ms. Of these patients, 11 males and five females had normal corrected QT intervals prior to starting treatment. In contrast, no cases of QT prolongation nor any significant changes to the QT intervals were noted in the control group (393.3 ± 36.1ms vs 387.4 ± 37.0ms; p=0.156). Donepezil was also found to increase the PR (177.0 ± 29.0ms vs 186.1 ± 34.2ms; p=0.04) and QRS (101.7 ± 20.3ms vs 104.7 ± 22.3ms; p=0.04) intervals, but no dose- or treatment duration-related differences were observed. Based on their findings, the authors recommended that ECG evaluation should take place before and after donepezil initiation.

## Regulatory actions taken by overseas regulatory agencies

In July 2021, the European Medicines Agency (EMA) assessed that donepezil may increase the risk of cardiac conduction disorders including QT prolongation and TdP.[5] Their review considered information from spontaneous adverse event reports and published literature. The EMA recommended for the addition of warnings on QT prolongation and TdP and interactions with other medicinal products known to prolong the QT interval to the package inserts (PIs) of donepezil products.

Similar updates on cardiac conduction disorders were made to the Australian PIs for donepezil following the Australian Therapeutic Goods Administration's (TGA) review of evidence from published literature and domestic and international post-market adverse event data.[6]

## Local situation

To date, HSA has not received any local reports of QT prolongation or TdP associated with donepezil. HSA is in the process of working with the product registrants to include warnings on QT prolongation and TdP in the local PIs of donepezil products.

## HSA's advisory

Healthcare professionals are advised to consider the risk of QT prolongation or TdP when prescribing donepezil to patients with pre-existing or family history of QT prolongation, relevant pre-existing cardiac disease (e.g., decompensated heart failure, recent myocardial infarction, bradyarrhythmias), electrolyte disturbances (hypokalaemia, hypomagnesaemia), or taking concomitant drugs known to affect the QT interval (Table 1). They may wish to consider ECG evaluation as part of the clinical monitoring of at-risk patients.

Table 1. Common drugs known to prolong QT interval

| Drug class | Examples |
|---|---|
| **Class IA antiarrhythmics** | Quinidine |
| **Class III antiarrhythmics** | Amiodarone, sotalol |
| **Antidepressants** | Citalopram, escitalopram, amitriptyline |
| **Antipsychotics** | Phenothiazine derivatives, sertindole, pimozide, ziprasidone |
| **Antibiotics** | Clarithromycin, erythromycin, levofloxacin, moxifloxacin |


## References

1. *Postgrad Med J 2021; 97: 452-458*
2. *Curr Cardiol Rev 2016; 12: 141-154*
3. *Ther Adv Drug Saf 2020; 11: 1-14*
4. *Clin Toxicol 2021; 59: 208-214*
5. *https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-5-8-july-2021-prac-meeting_en.pdf*
6. *https://www.tga.gov.au/publication-issue/donepezil-and-cardiac-conduction-disorders*

# FINASTERIDE AND POTENTIAL RISK OF SUICIDAL IDEATION

## Key Points

- Suicidal ideation is a known adverse event (AE) observed with the use of finasteride post-market and is listed in the local package inserts of finasteride-containing products
- A recent pharmacovigilance study suggested that younger patients with alopecia may be more vulnerable to the risk of suicidality; this association might be biased by stimulated reporting
- Healthcare professionals are advised to consider the potential risk of psychological AEs when assessing the benefit-risk of finasteride for their patients

Suicidal ideation is a known adverse event (AE) observed with the use of finasteride post-market and is listed in the local package inserts of finasteride-containing products. A recent pharmacovigilance study by Nguyen et al suggested that younger patients with alopecia may be more vulnerable to the risk of suicidality, although this association might be biased by stimulated reporting.[1]

Finasteride has been registered in Singapore since 1993. It is currently indicated for the treatment of benign prostatic hyperplasia and androgenic alopecia.

## Pharmacovigilance study of suicidality with finasteride

In the study, disproportionality analysis was used to assess whether suicidality or psychological adverse events were more frequently reported for finasteride than would be expected by chance alone by comparing them against similar reports for all other drugs in VigiBase, the World Health Organisation's global safety database. The study identified 356 reports of suicidality (suicidal ideation, attempted suicide, or completed suicide) and 2,926 reports of psychological AEs (depression or anxiety) in users of finasteride, reported from 1993 to 2019. Among the reports with data available, the majority (99%) occurred in males, and 71% occurred in individuals aged between 18 and 44 years. Significant disproportionality signals for suicidality (reporting odds ratio [ROR], 1.63; 95% CI, 1.47-1.81) and psychological AEs (ROR, 4.33; 95% CI, 4.17-4.49) were identified in finasteride users. In addition, when stratified by age and indication, younger patients less than 45 years old (ROR 3.47, 95% CI 2.90-4.15) and patients with alopecia (ROR 2.06, 95% CI 1.81-2.34) had significant disproportionality signals for suicidality that were not present in older patients or patients with benign prostatic hyperplasia. Conversely, this disproportionality in reporting of suicidality or psychological AEs was not observed for drugs with similar indications but different mechanisms of action (tamsulosin and minoxidil) or similar mechanisms of action and AE profiles (dutasteride).

The study also found that suicidality and psychological AE reports were highest in 2015 to 2019 (81.5% and 78.8%, respectively). Sensitivity analyses showed a disproportionate signal of reporting after the year 2012 (ROR, 2.13; 95% CI, 1.91-2.39), following widespread publicising of a potential link between finasteride and psychological morbidity. This suggests a reporting bias of stimulated reporting during these years that merits further investigation.

## International situation

In 2019, Health Canada completed its latest safety review on the risk of suicidal thoughts and/or behaviour in response to reported domestic and international cases of suicidal ideation and self-injury.[2] While the international reports, literature, and regulatory information reviewed could neither confirm nor deny a causal relationship between finasteride and suicide/self-injury, Health Canada concluded that there may be a link between finasteride and the risk of suicidal ideation and updated the Canadian product information to include a warning on this potential safety issue. Similar product information updates had also been implemented by the Australian Therapeutic Goods Administration, the European Medicines Agency[3], the United Kingdom's Medicines and Healthcare products Regulatory Agency[4] and the United States' Food and Drug Administration[5].

## Local situation

To date, HSA has received one report in 2014 of a 19-year-old male who developed severe mental depression with suicidal tendency after one month's use of finasteride 1mg. The patient recovered fully several weeks after stopping the medication.

The local package inserts of finasteride-containing products currently list depression and suicidal ideation as psychiatric AEs observed post-market.

## HSA's advisory

Mood alterations including depression and, less frequently, suicidal ideation have been reported in patients treated with finasteride. Healthcare professionals are advised to consider the potential risk of psychological AEs when assessing the benefit-risk of finasteride for their patients.

### References


1. *JAMA Dermatol. 2021;157(1):35-42*
2. *https://hpr-rps.hres.ca/reg-content/summary-safety-review-detail.php?lang=en&linkID=SSR00218#footnotes*
3. *https://www.ema.europa.eu/documents/psusa/finasteride-cmdh-scientific-conclusions-grounds-variation-amendments-product-information-timetable/00001392/201608_en.pdf*
4. *https://www.gov.uk/drug-safety-update/finasteride-rare-reports-of-depression-and-suicidal-thoughts*
5. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020788s030lbl.pdf*





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