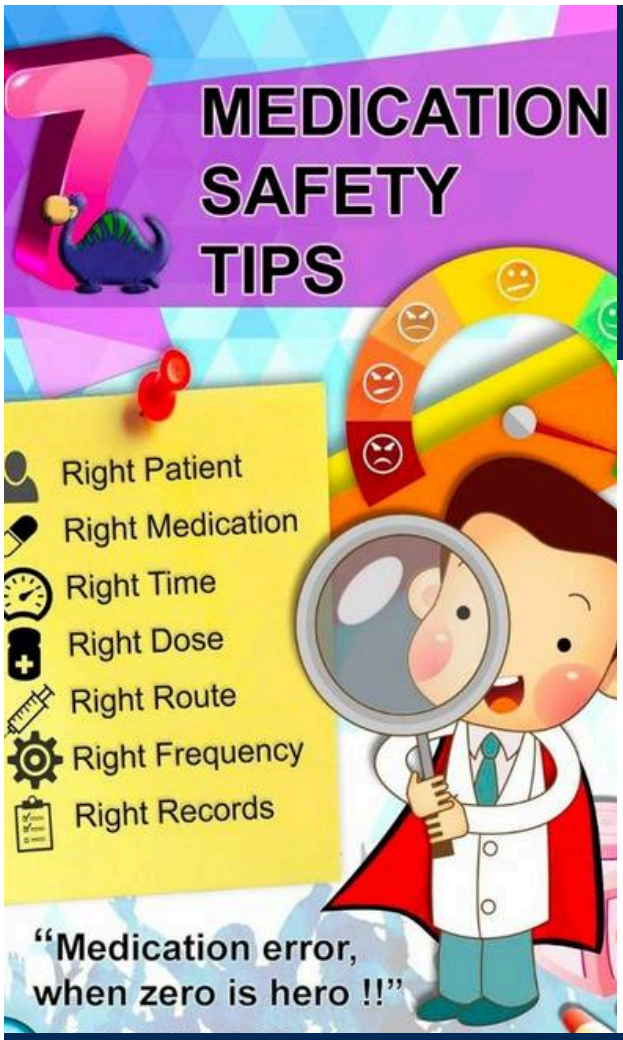

KEMENTERIAN KESIHATAN MALAYSIA
HOSPITAL ENCHE' BESAR HAJJAH KHALSOM

MEDICATION SAFETY BULLETIN YEAR 2026

MEDICATION SAFETY IS EVERYONE RESPONSIBILITIES

WHAT'S INSIDE?

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NPRA SAFETY ALERTS

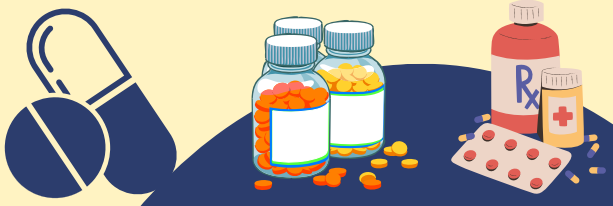
METFORMIN : RISK OF VITAMIN B12 DEFICIENCY

- Metformin is a biguanide antihyperglycaemic agent indicated for the treatment of type 2 diabetes mellitus and a reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG), and/or increased HbA1C.

- In Malaysia, there are currently 96 products containing metformin as a single active ingredient or a component of fixed-dose combination registered with the Drug Control Authority (DCA).

Safety Issue

- **Reduced vitamin B12 absorption with decreased serum level** was documented as **very rare** adverse effect of long treatment with metformin and **affect 1 in 10 people** who take metformin. This adverse effect of metformin was reassessed within Europe with input from the MHRA following a published literature which indicated that its frequency is higher than previously thought.
- The risk increases with a higher dose, longer treatment duration, and in patients with risk factors for vitamin B12 deficiency.
- A local study by Krishnan et al. (2020) indicates that the prevalence of vitamin B12 deficiency was substantially high (28.3%) among the metformin-treated population. In that study, race and duration of metformin use were reported as the most consistently associated factors with vit b12 deficiency. Non-Malay race (Chinese or Indian) was associated with an approximately 4-fold increased risk, whereas the duration of metformin use of more than 5 years conferred a greater than 2-fold increased risk for vitamin B12 deficiency.
- It is postulated that the mechanism underlying metformin-induced vitamin B12 deficiency has occurred mainly through changes in vitamin B12 absorption and metabolism, most possibly due to interference with calciumm - dependent absorption of the vitamin B12 - intrinsic factor complex at the terminal ileum.



A Word of Advice for Healthcare Personnel

- Both local and oversea studies revealed that metformin can commonly decrease serum vitamin B12 levels and lead to vitamin B12 deficiency.
- Be vigilant with the risk of vitamin B12 deficiency following metformin use as the risk increases with higher metformin dose, longer treatment duration and in patients with risk factors.
- Perform serum vitamin B12 level tests when metformin - induced vitamin B12 deficiency is suspected. Consider periodic vitamin B12 monitoring in patients with risk factors.
- Educate patients on metformin therapy to seek medical attention if they develop signs and symptoms suggestive of low vitamin B12 level, including new or worsening symptoms of extreme tiredness, a sore and red tongue, pins and needles sensation or pale or yellow skin.
- Treat vitamin B12 deficiency promptly in accordance with the latest clinical guidelines and continue metformin therapy for as long as it is tolerated and not contraindicated.
- Report all suspected adverse events associated with products containing metformin to the NPRA.

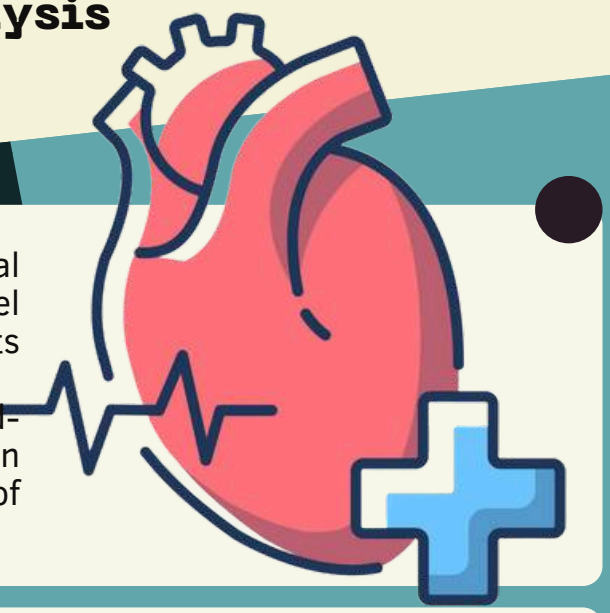
Adverse Drug Reaction Reports

The NPRA had received a total of 6,156 reports with 10,573 adverse events suspected to be related to metformin-containing products. The most frequently reported adverse events were diarrhoea (2,257), nausea (853), dizziness (806), vomiting (712), and pruritus (473). Of these, there were three (3) reports of anaemia vitamin B12 deficiency and one (1) report of vitamin B12 deficiency.

References: National Pharmaceutical Regulatory Agency (NPRA) (2024). Updated Metformin: Risk of Vitamin B12 Deficiency

STATINS (Atorvastatin, Rosuvastatin, Simvastatin): Interaction with TICAGRELOR Leading to Increased Risk of Rhabdomyolysis

STATIN AND TICAGRELOR



- Current guidelines recommend ticagrelor in dual antiplatelet therapy with aspirin over clopidogrel for prevention of stent thrombosis in patients with acute coronary syndrome (ACS).
- Moreover, in the management of ACS, lipid-lowering treatment with high-intensity statin therapy is advised for secondary prevention of cardiovascular events over the long term.

HOW DO THEY INTERACT?

Postulated mechanism:

- CYP3A4 isoenzymes
- Organic anion transporter polypeptide (OATPs)
- P-glycoprotein
- Glucuronidation

EVIDENCE WORLDWIDE

- A published analysis of VigiBase, the World Health Organisation (WHO) Pharmacovigilance Database, reveals statin and ticagrelor combination accounts for over a quarter of statin-related rhabdomyolysis cases received globally.
- Based on the multivariate analysis, the risk of rhabdomyolysis reporting was higher when ticagrelor was co-administered with atorvastatin (reporting odds ratios (ROR): 1.3) or rosuvastatin (ROR: 1.9). Conversely, such increased risk was not observed with other antiplatelets like aspirin, clopidogrel, or prasugrel.

CONSEQUENCE OF INTERACTION

- The **interaction** could result in many **unwanted adverse effects**. **Rhabdomyolysis is one of the most serious side effects.**
- Rhabdomyolysis is a severe form of muscle damage characterised by the release of sarcoplasmic proteins, such as aspartate aminotransferase, creatine kinase (CK) and electrolytes, into the blood circulation.
- Patients typically present with myalgia, muscle weakness, marked elevations of CK, myoglobinaemia, and/or myoglobinuria.

ADVICE FOR HEALTHCARE PROFESSIONALS

- Exercise caution and consider regular monitoring of CK and renal function in patients with risk factors for rhabdomyolysis including older age, male gender, prior elevated CK levels, diabetes, renal impairment, cardiovascular disease, use of high-dose statins or co-administration with certain interacting drugs.
- Educate patients to consult doctors if they encounter any signs and symptoms of muscle pain, tenderness or weakness.
- In cases of rhabdomyolysis under statin therapy, consider its association with ticagrelor. In such cases, consider temporarily suspending the statin, titrate to tolerated dose or switch to alternative agent.

References:

1. Mei, P. B. C. S. (2024, February 19). Statins (atorvastatin, rosuvastatin, simvastatin): Interaction with ticagrelor leading to increased risk of rhabdomyolysis. National Pharmaceutical Regulatory Agency (NPRA)
2. Danielak, D., Karaźniewicz-Łada, M., & Główka, F. (2018). Assessment of the risk of rhabdomyolysis and myopathy during concomitant treatment with ticagrelor and statins. Drugs, 78(11), 1105–1112. https://doi.org/10.1007/s40265-018-0947-x

by Nora Syafiqah

NPRA SAFETY ALERTS

LINEZOLID: RISK OF RHABDOMYOLYSIS

What is Linezolid?

Linezolid is an oxazolidinone-class antibiotic commonly used to treat infections caused by Gram-positive bacteria, particularly methicillin-resistant Staphylococcus aureus (MRSA). In Malaysia, there are currently eight registered products containing linezolid approved by the Drug Control Authority (DCA), available in both oral tablet form and as a solution for infusion.

What is Rhabdomyolysis?

Rhabdomyolysis is a clinical condition caused by the breakdown of skeletal muscle, which results in the release of intracellular components such as myoglobin, creatine kinase (CK), electrolytes, and sarcoplasmic proteins into the bloodstream. Patients commonly present with muscle pain, weakness, dark urine due to myoglobinuria and localized swelling. Diagnosis is mainly based on laboratory findings especially significantly elevated serum CK levels, often more than five times the upper normal limit.

SAFETY ALERT

- Information received by the National Pharmaceutical Regulatory Agency (NPRA) from the Japan PMDA highlights a potential risk of rhabdomyolysis associated with linezolid use.
- The proposed mechanism is that linezolid may cause mitochondrial dysfunction as mitochondrial ribosomes closely resemble bacterial ribosomes.
- This can inhibit mitochondrial protein synthesis leading to impaired cellular function with CK elevations serving as an early signal.

ADVERSE DRUG REACTION REPORTS

The NPRA has received 131 reports comprising 194 adverse events suspected to be associated with linezolid-containing products.

The most frequently reported events were thrombocytopenia (38), platelet count decreased (16), rash (9), maculo-papular rash (7) and vomiting (6). Of these, no reports were received associated with rhabdomyolysis.

ADVISE FOR HEALTHCARE PROFESSIONALS

- Be aware that rhabdomyolysis has been reported with linezolid therapy and should be considered in the differential diagnosis of patients presenting with muscle pain, weakness, dark urine or unexplained elevations in CK.
- For those on prolonged linezolid therapy, periodic monitoring of CK levels and early signs of muscle toxicity is recommended. In high-risk patients or those showing early adverse effects, alternative antibacterial therapy should be considered to reduce the risk of complications such as acute renal failure.
- If rhabdomyolysis is suspected, linezolid should be discontinued immediately, with supportive management including adequate hydration and close monitoring of renal function. All suspected adverse events related to linezolid-containing products should be reported to the NPRA.

References:
NPRA. (2026, February 10). *Linezolid: Risk of Rhabdomyolysis.*

NPRA SAFETY ALERTS

[UPDATED] SULFAMETHOXAZOLE, TRIMETHOPRIM (COTRIMOXAZOLE): RISK OF CIRCULATORY SHOCK

What is Cotrimoxazole?

Cotrimoxazole is a broad-spectrum antibiotic that combines sulfamethoxazole and trimethoprim, working synergistically to inhibit sequential steps in bacterial folate synthesis and produce a bactericidal effect. In Malaysia, there are currently 12 registered cotrimoxazole-containing products approved by the Drug Control Authority (DCA).

What is Circulatory Shock?

Circulatory shock is a life-threatening condition caused by acute circulatory failure leading to inadequate oxygen delivery, increased oxygen demand or impaired oxygen utilisation which results in tissue hypoxia, cell death, organ dysfunction, and ultimately multiorgan failure. Patients commonly present with hypotension, tachycardia, cold or clammy cyanotic skin, reduced urine output, confusion and disorientation although hypotension may be absent in the early stages due to compensatory mechanisms.

SAFETY ALERT

- Information received by the National Pharmaceutical Regulatory Agency (NPRA) from the European Medicines Agency (EMA) highlights a potential risk of circulatory shock associated with Cotrimoxazole use.
- The exact mechanism is not fully understood. Evidence suggests it does not involve a typical immunoglobulin E (IgE)-mediated anaphylactic reaction. Instead, a temporary increase in interleukin-6 (IL-6) points to a cytokine-driven inflammatory response which may explain why standard hypersensitivity treatments are often ineffective.

ADVERSE DRUG REACTION REPORTS

The NPRA has received 3,849 reports involving 6,955 adverse events suspected to be related to cotrimoxazole-containing products.

No cases of circulatory shock associated with cotrimoxazole have been reported locally.

ADVISE FOR HEALTHCARE PROFESSIONALS

- Be aware that circulatory shock has been reported with cotrimoxazole therapy, particularly in immunocompromised patients such as those with HIV and should be considered in patients presenting with fever, very low blood pressure or rapid heart rate.
- For patients receiving cotrimoxazole, educate them on the early signs of shock and advise prompt discontinuation of the drug with immediate medical attention if symptoms develop. Circulatory shock associated with cotrimoxazole may not respond to standard hypersensitivity treatments, including antihistamines, corticosteroids or adrenaline as the reaction is not IgE-mediated.
- All suspected adverse events related to cotrimoxazole-containing products should be reported to the NPRA.

References:
NPRA. (2026, February 10). *[Updated] Sulfamethoxazole, Trimethoprim (Cotrimoxazole): Risk of Circulatory Shock.*

NPRA SAFETY ALERTS

Vitamin B6 (Pyridoxine): Risk of Peripheral Neuropathy

What is vitamin B6?

Known as pyridoxine, is a water-soluble essential nutrient naturally present in many foods. It functions as a coenzyme in various enzymatic reactions, critical for neurotransmitter synthesis, haemoglobin formation, and the immune system.

Categories

Health supplements:

- maximum daily dose of 100 mg

Over-the-counter (OTC) medicines:

- daily doses exceeding 100 mg indicated for neurological and other disorders related to disturbances of metabolic functions influenced by the vitamin B complex

Safety Concern

- Supplemental intake has been associated with the development of peripheral neuropathy.
- Observed with high-dose or long-term use of vitamin B6-containing supplements, particularly when individuals consume multiple products containing pyridoxine.
- Symptoms of toxicity often resemble those of vitamin B6 deficiency.

ADR Reports

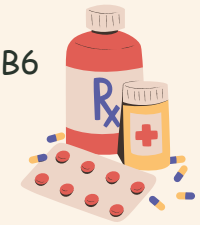
- NPRA received 1,156 reports following the use of health supplements or OTC products with vitamin B6.
- No local ADR reports of neuropathy or peripheral neuropathy was received but related adverse events, such as tingling were reported with Vitamin B1/B6/B12 products.
- Although international evidence shows that neuropathy may occur but no local data confirmed cases linked solely to vitamin B6, considering additional active ingredients and underlying conditions.

Advice for Healthcare Professionals

- Be aware that neurological adverse events have been associated with the administration of vitamin B6, including at low doses.

- Advise patients to stop taking vitamin B6 and consult a doctor if they experience symptoms of peripheral neuropathy.

- Advise patient to check the vitamin B6 content in each product and to be mindful of their total daily intake.



- Report all suspected adverse events associated with vitamin B6-containing products to the NPRA.

References

1. National Pharmaceutical Regulatory Agency. (2026). Vitamin B6 (Pyridoxine): Risk of Peripheral Neuropathy. Retrieved from: https://www.npra.gov.my

by Haziq Izzuddin

NPRA SAFETY ALERTS

FINASTERIDE AND DUTASTERIDE: RISK OF SUICIDAL THOUGHTS

SAFETY CONCERNS

Suicidal ideation

Depression

Sexual dysfunction

A pharmacovigilance case series of six suicide cases in men treated with finasteride for AGA found persistent sexual dysfunction and insomnia were commonly reported, with no pre-existing medical or psychiatric conditions.

SOURCE OF SAFETY CONCERNS

NPRA received information from the **European Medicines Agency (EMA)** following its review of finasteride and dutasteride in relation to the risk of suicidal ideation. The EMA's **Pharmacovigilance Risk Assessment Committee (PRAC)** confirmed adverse effect of **suicidal ideation** associated with both the 1 mg and 5 mg oral finasteride, although its frequency is unknown. Nevertheless, the committee maintained that the overall **benefit–risk balance** of both finasteride and dutasteride **remains positive.**

PRODUCT OVERVIEW

Both are 5α-reductase inhibitors that block the conversion of testosterone to dihydrotestosterone (DHT), a key hormone involved in both androgenetic alopecia (AGA) and benign prostatic hyperplasia (BPH). These medicines help slow hair loss, promote hair regrowth, and reduce prostate size.

INDICATION

Finasteride oral 1 mg formulation and topical spray is approved for the treatment of male pattern hair loss (AGA).

Oral 5 mg finasteride and dutasteride are indicated for the treatment and management of BPH.

LOCAL ADR REPORTS

To date, the NPRA has received **164** reports involving **240** adverse events suspected to be associated with finasteride-containing products, and **80** reports involving **122** adverse events related to dutasteride. No cases of suicidal ideation or depression have been reported for either product. However, there have been 14 reports of sexual dysfunction associated with finasteride and 13 reports with dutasteride.

ADVICE FOR HEALTH CARE PROFESSIONALS

Be vigilant of the risk of suicidal ideation associated with the use of both 1 mg and 5 mg finasteride.

Be aware of the risk of sexual dysfunction which may contribute to psychiatric adverse events.

Educate patientswho are on **5 mg finasteride for benign prostatic hyperplasia (BPH)** to seek medical advice as soon as possible if they experience psychiatric symptoms

Advise patients who are on **1 mg finasteride for androgenetic alopecia (AGA)** to discontinue treatment and seek medical attention promptly if they develop psychiatric symptoms

Inform patients of the potential risk of psychiatric adverse events and advise them to report any mood changes or suicidal thoughts immediately.

Monitor patients with a history of psychiatric disorders closely when prescribing finasteride or dutasteride.

Report all suspected adverse events related to the use of finasteride- or dutasteride-containing products to the NPRA.

REFERENCE

1. National Pharmaceutical Regulatory Agency. (2025). Finasteride and Dutasteride: Risk of Suicidal Thought. Retrieved from: https://www.npra.gov.my

PRESCRIPTION OPIOID: RISK OF OESOPHAGEAL DYSFUNCTION

NPRA SAFETY ALERTS

Opioids are potent analgesics with established therapeutic indications for the management of acute pain, post-surgical pain and cancer-related pain. In Malaysia, prescription opioids are approved for a range of clinical uses, including the management of moderate to severe pain, as an adjunct to anaesthesia for analgesia, and for the treatment of opioid addiction.

Opioid-induced oesophageal dysfunction (OIED)

OIED is an oesophageal motility disorder and is diagnosed by abnormal manometric testing in individuals who have been receiving daily opioid therapy for a minimum of three (3) months.

It is characterised by manometric findings such as Type III achalasia, oesophagogastric junction outflow obstruction, distal oesophageal spasm, and hypercontractile oesophagus.

Symptoms of OIED

Source of safety concern

The safety review was triggered by Health Canada following signals identified in published scientific literature on OIED, including cases with diagnoses confirmed by oesophageal pressure testing, and included an assessment of post-marketing reports from the Canadian Vigilance database.

SAFETY ISSUE

The exact mechanism of opioid-induced oesophageal dysfunction (OIED) is unclear, but it is thought that chronic opioid use disrupts inhibitory neural pathways, leading to unopposed excitatory activity. This results in abnormal oesophageal contractions and impaired relaxation of the lower oesophageal sphincter (LES).

OIED is more common with stronger opioids (e.g., oxycodone 31%, hydrocodone 28%) compared to weaker ones like tramadol (12%). It is also dose-related, with higher median daily doses (45 mg vs 30 mg morphine equivalent) seen in affected patients.

Reported cases involved opioid doses of 30–300 mg morphine daily (median 67.5 mg), with symptoms typically developing after weeks to months of continuous use.

Advice for Healthcare Professionals

- While NPRA is still reviewing this safety issue, be aware of the risk of OIED when prescribing long-term opioid therapy.
- Educate patients to seek medical advice if they experience the common symptoms of OIED such as difficult swallowing, gastroesophageal reflux, or chest pain.
- If a patient develops symptoms associated with OIED, the first therapeutic measure to be considered is opioid withdrawal, and the clinical response should be assessed.
- Evidence suggests OIED is more common with stronger opioids and higher daily opioid doses. Consider using the lowest effective dose for the shortest duration, and regularly reassess the ongoing need for opioid therapy.
- Report all suspected adverse events associated with opioid-containing products to the NPRA.

Local Adverse Drug Reaction Reports

The NPRA has received 6,867 reports with 11,676 adverse events suspected to be related to products containing prescription opioids. There have been no local reports of OIED or any oesophageal-related disorders associated with opioid use.

Reference

National Pharmaceutical Regulatory Agency (NPRA). (2026, January 22). Prescription opioid: Risk of oesophageal dysfunction. Ministry of Health Malaysia

PROGESTOGENS : RISK OF MENINGIOMA

Progestogens or gestagens, can be either natural or synthetic (referred to as progestins) compounds that bind to progesterone receptors and mimic effects of progesterone.

EXAMPLES
- Cyproterone Acetate,
- Medroxyprogesterone Acetate,
- Chlormadinone

PROGESTOGEN

It used to treat various gynaecological conditions, such as endometriosis, fibroids, prolonged or heavy periods, and menstrual cycle disorders. Additionally it being used in hormone replacement therapy, including menopausal hormone therapy, as well as in obstetrics for conditions like luteal insufficiency-related sterility and recurrent abortions.

MENINGIOMA

slow-growing, non-cancerous tumours that can still exert pressure on nearby brain tissue, potentially necessitating surgical interventions.

RISK FACTOR (WITH SHARP RISE AFTER 65 Y/O
- female sex,
- neurofibromatosis type 2, and
- exposure to ionising radiation

SAFETY ISSUE

In 2020, the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA) confirmed a **cumulative dose-dependent association between cyproterone acetate and the risk of meningioma.** While the risk is considered rare overall, it is most pronounced at doses of 25 mg per day and higher.

In 2022, the EMA confirmed that nomegestrol and chlormadinone are also associated with an increased risk of meningioma, particularly when used at high doses (3.75-5 mg for nomegestrol and 5-10 mg for chlormadinone) and over prolonged periods of use.

Recent evidence from a large French epidemiological study (2009–2018) has shown that prolonged use (≥1 year) of certain progestogens—specifically medrogestone,injectable medroxyprogesterone acetate (MPA), and promegestone—is associated with an increased risk of meningioma, reinforcing previously known risks with cyproterone acetate, nomegestrol acetate, and chlormadinone acetate.

Local product registration and ADR Reports

The NPRA has received a total of 772 ADR reports related to progestogen products locally registered with the Drug Control Authority (DCA). Notably, no local cases of meningioma have been received among the submitted reports.

ADVISE TO HEALTHCARE PROFESSIONALS

- **Be aware of the potential risk of meningioma when initiating any progestogens:**
  - **Cyproterone acetate and chlormadinone are known risk factors for meningioma, particularly with cumulative high doses.**
  - **As a precautionary measure, medroxyprogesterone acetate containing products (all injectables and oral dosage of ≥100mg) are contraindicated in patient with meningioma or history of meningioma (for non-oncological indications).**

- **Be attentive to any previous progestogen use when prescribing new progestogens. Avoid using progestogens with reported risks of meningioma in patients with a history of meningioma or existing meningioma.**
- **In exceptional cases, progestin treatment may be considered after a thorough evaluation in a multidisciplinary consultation, weighing the individual benefit-risk ratio and the availability of alternatives**

- **Always prescribe progestogen at the minimum effective dose and for the shortest duration necessary.**
- **Educate patients to contact their doctor immediately if they experience a change in vision (seeing double or blurriness), hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures, or weakness in their arms or legs.**
- **Vigilantly monitor high-risk patients for signs and symptoms of meningiomas in line with clinical practice. Consider a brain Magnetic Resonance Imaging (MRI) if meningioma is suspected.**

- **If a meningioma is diagnosed, consider discontinuing treatment with these progestogens permanently.**
- **Report all suspected adverse events associated with progestogen-containing products to the NPRA.**

REFERENCES

National Pharmaceutical Regulatory Agency (NPRA). (2025, September 17). [Updated] Progestogens (cyproterone acetate, medroxyprogesterone acetate, chlormadinone): Risk of meningioma. Ministry of Health Malaysia. https://www.npra.gov.my/index.php/en/industry/more-regulations/recent-updates/465-english/safety-alerts-main/safety-alerts-2025/1527763-updated-progestogens-cyproterone-acetate-medroxyprogesterone-acetate-chlormadinone-risk-of-meningioma.html

by Nur Alifah Iiyana

NPRA SAFETY ALERTS

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS) AND SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS): RISK OF PERSISTENT SEXUAL DYSFUNCTION

SAFETY ISSUE

SSRIs and SNRIs have been associated with persistent sexual dysfunction after discontinuation, known as post-SSRI sexual dysfunction (PSSD). Reported effects in both men and women include reduced libido, erectile dysfunction, orgasm difficulties, genital numbness, painful intercourse, and prolonged erections.

These effects may last weeks to years, are likely underreported, and can impact quality of life. The TGA now requires all product information to include this risk.

ADVERSE DRUG REACTION REPORTS

NPRA has received 1,399 reports comprising 2,815 adverse events suspected to be associated with SSRI- and SNRI-containing products. The most frequently reported events were nausea, headache, and dizziness.

Of these, 22 reports involved sexual dysfunction. However, no information on persistent sexual dysfunction was identified in the reported cases.

REGULATORY ACTIONS

The NPRA reviewed the risk of persistent sexual dysfunction with SSRIs/SNRIs and on 7 October 2025, directed all product holders to update package inserts with this safety information.

ADVICE FOR HEALTHCARE PROFESSIONALS

- Remain vigilant for persistent sexual dysfunction with SSRI/SNRI use, which may continue after discontinuation in both males and females.
- Proactively counsel patients on this potential risk, advise them to monitor for symptoms, and encourage prompt reporting of such events.
- Actively inquire about symptoms such as reduced sexual desire, erectile difficulties, problems with orgasm, genital or nipple numbness, painful intercourse, or prolonged erection.
- If sexual dysfunction is reported, review SSRI/SNRI use and assess for other causes such as age, smoking, alcohol/substance use, and conditions like diabetes, hypertension, or depression.
- Consider discontinuation or switching therapy based on clinical judgement. Report suspected SSRI/SNRI adverse events to NPRA.

REFERENCES

Seksyen Farmakovigilans. (2025, November 14). Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs): Risk of Persistent Sexual Dysfunction. Npra.gov.my.

NPRA SAFETY ALERT

Angiotensin II Receptor Blockers (ARBs): Risk of Intestinal Angioedema

SAFETY ISSUE

Intestinal angioedema (ARB-related) is a condition with submucosal fluid in the intestinal wall causing abdominal pain, nausea, and vomiting, often mimicking acute abdomen and leading to unnecessary surgery. Diagnosis is challenging due to non-specific symptoms. It has been reported with ARB use, likely due to angiotensin II receptor type 1 blockade causing increased angiotensin II receptor type 2 stimulation and bradykinin-mediated effects.

The NPRA has received updates from the European Medicines Agency (EMA) regarding the risk of intestinal angioedema associated with ARB use. A total of 45 cases of intestinal angioedema were identified, involving olmesartan, olmesartan/ hydrochlorothiazide, olmesartan/ amlodipine, candesartan, irbesartan, losartan, valsartan and valsartan/sacubitril. Although not all ARBs were involved, it is considered a class effect, supported by similar reactions seen with ACE inhibitors.

LOCAL ADVERSE DRUG REACTION REPORTS

To date, the NPRA has received a total of 3,437 adverse drug reactions reports with a total of 6,022 adverse events associated with ARB use in Malaysia.
Currently , most ACEI package inserts (PI), including those for enalapril, lisinopril, perindopril, and ramipril, specifically mention “intestinal angioedema”. However, most ARB PIs generally list “angioedema” without specifying the intestinal form.

ADVICE FOR HEALTHCARE PROFESSIONALS

- Be aware that intestinal angioedema has been reported with ARBs, including olmesartan, irbesartan, valsartan, losartan, and candesartan. Caution should also be taken with other ARBs.
- Educate patients to seek medical advice if they have symptoms such as abdominal pain, nausea, vomiting, and diarrhoea.
- Consider performing radiological assessments such as abdominal CT scans or ultrasonography in patients on ARBs presenting with abdominal pain.
- If intestinal angioedema is suspected, discontinue the ARB and monitor the patient until all symptoms have completely resolved. Report all suspected adverse events related to ARBs-use to the NPRA.

REFERENCE
Seksyen Farmakovigilans. (2025, May 28). Angiotensin II Receptor Blockers (ARBs): Risk of Intestinal Angioedema. Npra.gov.my

by Siti Nur Aisyah

Medication Error in HEBHK: Case Sharing (2025)

Case 1 - Actual Error (Prescribing Error)

Brief summary of the incidents and the patient's outcome	Patient was on IVI Dobutamine, endorsed as 20mcg/kg/min, run at 144ml/hr. The infusion rate should be 7.2ml/hr and may up to 14.4ml/hr (for maximum dose of 40mcg/kg/min). Intervention was done by pharmacist via phone call, supplied to ward as per intervention dose due to emergency cases. However, no documentation or re-endorsement of prescription done in ward, thus suspected of dosage error. Error outcome category E = Treatment/intervention - caused temporary harm.
Location of event	Hospital – In ward (Medical)
Sequence of events	25/01/2025 -Morning review, patient's BP borderline. Hence, started on IVI Noradrenaline. -Blood investigation: worsening AKI and metabolic acidosis, worsening transaminitis (severe). Intubated at 8pm. Post intubation, inotropic support increasing and started on 2nd inotrope (IVI Dobutamine 5mcg/kg/min) and titrated accordingly overnight. 26/01/2025 -ABG worsening metabolic acidosis, added on IVI Adrenaline and titrated up IVI Dobutamine to 20mcg/kg/min. -Prescription endorsed as 20mcg/kg/min, but the dilution 144ml/hr was wrong. -Informed by pharmacist that dilution for IVI Dobutamine 20mcg/kg/min (7.2ml/hr) while maximum dose 40mcg/kg/min (14.4ml/hr). -Prescriber agreed with pharmacist and requested to provide for maximum dose 40mcg/kg/min (14.4ml/hr) as BP is still borderline and might need to titrate up further. -After supplied, new dose informed to ward to alert staff nurse however no documentation or re-endorsement done by prescriber in ward. Suspected of wrong dose administered.
Contributing factors, root cause(s)	1. Verbal communication issue – Miscommunication between staff nurse, doctor and pharmacist. 2. Lack of knowledge regarding dilution of inotropic support. 3. Heavy workload 4. Wrong infusion pump setting, medication related issue.
Corrective and preventive actions taken by facility	1. CME conducted regarding the guidelines for dilution of inotropic medications. 2. Flip charts / cards on the dilution of inotropic medications displayed in the ward or placed on medication trolley. 3. Infusion pump training conducted. 4. Reminder to staffs to communicate with proper language and provide proper documentation for every treatment plans or details.

Medication Error in HEBHK: Case Sharing (2025)

Case 2 - Near Miss (Prescribing Error)

Brief summary of the incidents and the patient's outcome	**Patient discharged from ward with wrong dose of oral Fluconazole. In ward, patient was on IV Fluconazole 200mg OD, however upon discharged prescribed with oral Fluconazole 400mg TDS (wrong dosage and higher than usual dose) which renal adjusted dose should be oral Fluconazole 200mg OD. During intervention by pharmacist, prescriber unsure the dose as dose started as advised by AMS team. During discussion with AMS team, informed that no plan to change to oral or discharge. The discharged plan was made by surgical team, thus the process to prepare medication for discharged patient took longer time.** **Error outcome category A = Potential error, circumtances/events have potential to cause incident**
Location of event	Hospital – In ward (Surgical)
Sequence of events	30/04/2025 – 09/05/2025 -Patient admitted with fever and pus discharge from left percutaneous nephrostomy (PCN). Urine C&S Candida Albicans – started with IV Fluconazole 200mg OD as per advised by AMS team. 09/05/2025 -Pharmacy received discharged prescription with oral Fluconazole 400mg TDS – called up prescriber for confirmation of dosage. However, MO not sure the dose as it was planned by AMS team. -Pharmacist tried to reach AMS team via phone call but no answer, also no reply when texted personally. -Pharmacist discussed with physician regarding dosage of oral Fluconazole but physician requested to consult AMS team for better outcome. -Pharmacist updated progress to prescriber, however MO requested to liaise with another MO as already off-duty. -Discussion continued with MO on-call and dose changed to Oral Fluconazole 200mg OD (renal adjusted dose).
Contributing factors, root cause(s)	1. Oral Fluconazole rarely used at General Surgery Department. 2. No proper work flow on cases that had been reviewed by AMS team upon discharge home.
Corrective and preventive actions taken by facility	1. Create proper work flow regarding action need to be taken for discharging patients who had been reviewed by AMS team. 2. Provide notice of order pertaining information counter for dosage of drugs to all medical officer as well as to write down eGFR on the prescription for patient who have kidney disease.

Medication Error in HEBHK: Case Sharing (2025)

Case 3 - Actual Error (Administration Error)

Brief summary of the incidents and the patient's outcome	**Incident happened whereby there was confusion in giving IV Vancomycin to patient resulting in TDM vancomycin reached toxic level. Investigation noted that IV Vancomycin 2.25g (antibiotic-lock therapy) that was supposed to be given on 04/07/2025 was signed by SN on 07/07/2025, 8pm. In addition, MO officer who reviewed patient on 07/07/2025 written to continue IV Vancomycin and IV Vancomycin that was prescribed on drug chart did not have date on resulting in misinterpretation by SN.** **Error outcome category D = Additional monitoring required - caused no harm.**
Location of event	Hospital – In ward (Medical)
Sequence of events	<u>03/07/2025</u> -During morning review, for IV Vancomycin lock post guidewire exchange and HD next day. <u>04/07/2025</u> -Suggested for IV Vancomycin 2.25g post HD. To repeat TDM on 06/07/2025, 6am with random sample. -Patient did HD 4 hours. No vancomycin-lock written in entry. <u>06/07/2025</u> -TDM below detectable range likely antibiotic was not served. -Pharmacist asked for confirmation from SN and be informed that IV Vancomycin was given as per instructed, thus suggested to serve IV Vancomycin 1.5g STAT and repeat TDM on 08/07/2025, 6am with random sample. -Result TDM was not taken by ward until it was sent to ward on next working day. <u>07/07/2025</u> -IV Vancomycin 2.25g (antibiotic-lock therapy) that was supposed to be given on 04/07/2025 was signed by SN on 07/07/2025, 8pm which means that IV Vancomycin was not served on 04/07/2025. -MO officer who reviewed patient on 07/07/2025 written to continue IV Vancomycin and IV Vancomycin 2.25g post HD that was prescribed on drug chart did not have date on resulting in SN misinterpreting that IV Vancomycin need to be served on 07/07/2025. <u>08/07/2025</u> -TDM showed toxic level. Pharmacist suggest to withheld IV Vancomycin and repeat TDM on 11/07/2025, 6am with random sample.
Contributing factors, root cause(s)	1. Documentation in patient's record not accurate leading to wrong interpretation on IV Vancomycin. No date written on IV Vancomycin on drug chart. 2. Staffs at General Medicine Department not well verse with Vancomycin lock therapy and IV Vancomycin.
Corrective and preventive actions taken by facility	1. CME pertaining to antibiotic lock therapy was given to physicians as well as medical officers by pharmacist. 2. CNE at department level pertaining antibiotic lock therapy. 3. Notice of order whereby antibiotic lock therapy need to be prescribed in drug chart and that drug chart need to be taken down to HDU.

Medication Error in HEBHK: Case Sharing (2025)

Case 4 - Near Miss (Dispensing Error)

Brief summary of the incidents and the patient's outcome	**Floor stock of ward was wrongly given. Ordered for 20 tablets Perindopril 4mg but the bottle was filled with 20 tablets Pantoprazole 40mg.** **Error outcome category B = Actual Error - did not reach patient**
Location of event	Hospital – Pharmacy (In-patient)
Sequence of events	08/08/2025 -Ward indent floor stock Tab. Perindopril 4mg (20's). Empty bottle was sent to pharmacy. -Pharmacist assistant filled the bottle with 20 tablets Pantoprazole 40mg. Medications was taken based on physical appearance without reading the label. -Pharmacist counter-checked medications only through the bottle without taking out the tablets and did not read the label properly. -Medication were brought back to ward by SN without checking at pharmacy. 11/08/2025 -SN noted medications inside the bottle was Tab. Pantoprazole 40mg instead of Tab. Perindopril 4mg. -Medications were returned to Inpatient Pharmacy for exchange.
Contributing factors, root cause(s)	1. Pharmacy staffs filled and checked the medications based on appearance of the medications and did not properly read the label. 2. UOD label of Tab. Pantoprazole 40mg was same as Tab. Perindopril 4mg, it was not well communicated to all pharmacists. 3. Lack of staff nurse in ward leading to the need of checking medications only at ward, but not at the pharmacy.
Corrective and preventive actions taken by facility	1. Reminder to all pharmacists to read the label of UOD before filling / dispensing medications to patients / wards. 2. Explanation letter from the involved staff as well as reprimand letter to the involved staff. 3. Bed-side teaching pertaining SOP of taking medications stock from Pharmacy Department. 4. Announcement of change of UOD label of Tab. Perindopril 4mg were made and from time to time when there is change of UOD label. 5. Application for additional staff nurse done and sent to higher authority.

Medication Error in HEBHK: Case Sharing (2025)

Case 5 - Actual Error (Prescribing Error)

Brief summary of the incidents and the patient's outcome	**Patient was informed to take 5 tablets of Apixaban instead of 1 tablet. During admission, patient was told to continue own medication Tab. Apixaban 2.5mg BD, however medication prescribed on drug chart was Tab. Apixaban 25mg BD. As family member enquired if having any dosage change, staff nurse went through the drug chart and informed to take 5 tablets (which equal to 12.5mg due to wrong calculation). Despite that, patient was overdose even with lesser dose than prescribed in drug chart. Error outcome category D = Additional monitoring required - caused no harm**
Location of event	Hospital – Ward (Medical)
Sequence of events	<u>01/08/2025</u> -Patient admitted to ward. Restarted with old medications including Tab. Apixaban 2.5mg BD (own medication). -Wrong dose of Tab. Apixaban written on drug chart (25mg BD). <u>03/08/2025</u> -Family member enquired the dosage (number of tablets need to be taken), SN informed to take 5 tablets of Apixaban (dose = 12.5mg) after going through the drug chart. -During ward round, specialist noted patient took wrong dose of Tab. Apixaban – no bleeding tendencies. The correct dose was informed to family member (to be taken 1 tablet only). -Patient was given activated charcoal 100g STAT for reversal.
Contributing factors, root cause(s)	1. Staff at General Medicine Department not well verse with Tab. Apixaban as it is not frequently used in our hospital.
Corrective and preventive actions taken by facility	1. CME pertaining to oral anticoagulant at department level for all categories of staff.

Medication Error in HEBHK: Case Sharing (2025)

Case 6 - Actual Error (Administration Error)

Brief summary of the incidents and the patient's outcome	**Patient was given IV Rocuronium instead of IV Tranexamic Acid during elective caesarean section procedure as patient bled with estimated blood loss around 600ml. Post administration, GCS dropped to $E_4V_1M_1$ (blank stare) and unresponsive to call. Subsequently proceeded with intubation for airway protection. Post intubation, hemodynamically were stable.** **Error outcome category E = Treatment/intervention - caused temporary harm**
Location of event	Hospital – Operation theatre
Sequence of events	15/10/2025 -Patient undergone elective caesarean section for placenta previa type 3 and transverse lie. After baby delivered, patient bled with estimated blood loss around 600ml. -Surgeon requested for IV tranexamic acid and IM Hemabate STAT. -Few seconds post administration of drug, GCS dropped to $E_4V_1M_1$ (blank stare) and unresponsive to call. Patient become tachycardia and hypertensive while SPO_2 remained 100%. -Call for help to anesthetist and preparing to intubate patient as GSC was $E_1V_1M_1$, unresponsive, pupil equal, weak cough & gag reflex, no spontaneous breathing and SPO_2 dropped to lowest 88%. -Subsequently, proceeded with intubation and was intubated successfully. Post intubation, hemodynamic were stable. -Specialist reviewed all the medications given to patient and found out an empty vial of Rocuronium and there was a vial of Tranexamic Acid which was not been syringed out. -Towards the end of operation, noted patient having spontaneous breathing and able to follow simple command. -IV Sugammadex was given for reversal. Patient then extubated successfully.
Contributing factors, root cause(s)	1. MO was preparing drug for next case while current case still ongoing. Anesthetic assistant was not called to assist in preparing drugs during event. 2. Shortage of medical officer led to increase in workload and number of on-calls per month.
Corrective and preventive actions taken by facility	1. Service closure (eg: epidural service) by anesthetist due to shortage of human resource to prevent burn out. 2. Request for addition / adequate number of MO in the department. 3. Case discussion during Mortality & Morbidity meeting. 4. Establish peer support group during department CME and reminder to seek superior help when needed.

Medication Error in HEBHK: Case Sharing (2025)

Case 7 - Actual Error (Administration Error)

Brief summary of the incidents and the patient's outcome	**S/C Fondaparinux 2.5mg OD was administered to wrong patient which was not intended to be given the medication.** **Error outcome category D = Additional monitoring required - caused no harm**
Location of event	Hospital – In ward (Medical)
Sequence of events	25/09/2025 -Patient admitted due to alleged herbicide ingestion with underlying paraphrenia, under psychiatric follow-up. 02/10/2025 -SN who done double shift that day came to serve S/C Fondaparinux to patient, however family member told that patient never had any injection previously. SN told that medication usually be given to obese or older patient, thus family member agreed. -Drug chart with endorsement of S/C Fondaparinux was brought and signed by SN however SN did not checked patient's name. -During evening round by MO Psy, SN noticed of wrong patient been administered with S/C Fondaparinux previously. Informed MO and family member, also explained on the risk of bleeding and for family member to report immediately if any. -Close monitoring was done and no complained received from patient or family member. 03/10/2025 -Close monitoring was continued and no adverse events reported. -Patient requested for AOR discharge.
Contributing factors, root cause(s)	1. SN did not practice two-identifiers during administration of drug. 2. Shortage of staffs in ward led to increase in workload and number of shifts per month. 3. No double-checking of medication prepared done by second personel prior to administration to patient.
Corrective and preventive actions taken by facility	1. Reminder to all staffs pertaining importance of practicing two-identifiers to avoid any unwanted incidents. 2. Request for addition staffs in the department.

PHARMACY

TIPS TO ACHIEVE ZERO DISPENSING ERROR

- Reconfirm patient's details with the prescription.
- Check if the prescribed drugs are the same as the prepared drugs
- Avoid getting distracted while dispensing.
- Interpret the prescription order clearly.
- Avoid dispensing medications when not feeling well.
- Engage with patients well to prevent medication errors.

QUICK GUIDE: PREVENTING PRESCRIPTION ERROR

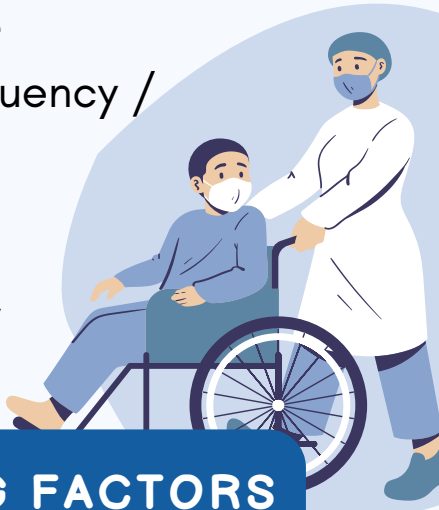
TYPES OF PRESCRIPTION ERROR

1. PRESCRIPTION ERROR

- Error prone abbreviation
- Calculation error
- Inappropriate dose
- Wrong route / frequency / medication name

2. WRONG MEDICATIONS

- Inappropriate polypharmacy



WHAT ARE THE MAIN CONTRIBUTING FACTORS TO PRESCRIPTION ERROR?

- Lack of knowledge on medication in relation to clinical use.
- Lack of knowledge on patient safety and medication safety.
- Lack of knowledge on safe prescribing.
- Not following SOP (Good Prescribing Practice).
- Use of abbreviation.
- Illegible handwriting
- “Assume culture” (i.e. take action based on the assumption without verification).
- Communication breakdown among team members. Example – Unclear instruction.
- Reluctant to confirm with superior before prescribing.
- Human factor – staff fatigue, stress, overwork and heavy workload.

Quick Guide_ Preventing Prescription Error

WAYS TO PREVENT PRESCRIBING ERROR

BEFORE

Know

1. Patient medical history, current illness and diagnosis
2. Patient current medication and allergies
3. Medication side effect, contraindication and safe dosage

Check

1. Patient identity using two identifier.
2. Information about patient medication from other healthcare facility.
3. Medication information- dose, indication, contraindication using reliable guidelines. (Eg: Ministry of Health Clinical Practice Guidelines, MIMS, MOH Formulary (Blue book), National Antibiotic Guideline etc.

Ask

Advice from other staff, superior, pharmacists and clinical pharmacists if you are unsure about medications interaction or other aspects of prescribing and medicines management.

DURING

- Preferably use **BLOCK LETTERS** when prescribing. Make sure the writing is legible
- **Do not use ABBREVIATION OR ACRONYM**. Except for acceptable standard of abbreviation
- Use **GENERIC NAME** instead of Brand names of the medication.
- Use **LEADING ZERO** before decimal point. Write "zero" before the decimal point.
- Avoid **TRAILING ZERO** after decimal point. Do not write "zero" after decimal point.
- Use mcg or microgram and not using symbol (µg).
- Limit number of medications in one medication slip(outpatient), **maximum 5 medications in one slip** and make sure to write a page number for every prescription slip if it involves more than 1 page.
- When prescribing infusion drug, please write clear instruction regarding **dose, route and rate of infusion.**
- It is recommended to **prepare a list of common drug with dosage, frequency, route** in wards and clinics.
- **Identify patient correctly using two identifier.** Identify patient correctly using two identifier. (example: patient's full name, IC No and MRN). ** If patient is unconscious or not mentally-stable; use IC No, MRN, and face recognition in IC compared to patients face or input from family members.
- Always **take note of allergy, contraindication, body weight and body surface area** for specific medication such as chemotherapy.
- **Double check** with superior or senior colleague if not sure about the name of medication, dose of medication, route of medication, frequency of medication and duration.
- Make sure you have **references** either manual booklet or phone application that you can always refer to before making a prescription.
- Avoid giving verbal order.
- It is recommended to prepare a list of common medication or calculation on dosage for high risk patients such as paediatric patient or patient with renal impairment in ward and clinics.

AFTER

- Monitor medication chart regularly
- For in-patient, remember to CANCEL existing prescribed medication after completing its course. For example:

Antibiotics usually given for certain duration. Doctor must always remember to "CANCEL" medication in medication chart after completing the course of antibiotics. New type of medication is prescribed to replace the existing medication

- When patient is about to be discharged, make sure the list of medication written on prescription is updated and similar with the list of medications written on discharge note

References:

- Medication Errors Observed In 36 Healthcare Facilities, 2002. Archives of Internal Medicine,162:1897-1903.
- Quick Reference for Healthcare Providers, Good Prescribing Guidelines, 2014. Pharmaceutical Services Division Penang State Health Department.

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