Ministry of Health Malaysia
HOSPITAL PUTRAJAYA

Pharmacy Bulletin

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Pharmacy Department, Hospital Putrajaya

Caring For You and About You

DO YOU KNOW?

Caffeine may improve the analgesic effect of Paracetamol. Even, formulation of Paracetamol with caffeine is commercially available in Malaysia.

However the extent of analgesic effect remains uncertain. Thus it is advisable to counsel patients and caregivers to take into account the dietary and other medicinal sources of caffeine, if Paracetamol with Caffeine is to be consumed; so as not to exceed the recommended maximum daily dose of Caffeine (520mg per day).

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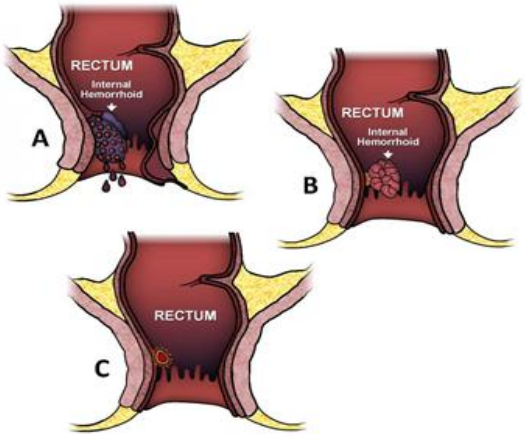
EDITORIAL BOARD

HEMORRHOIDS

By: **NOR AINAA BINTI AB RAZAK**



EPIDEMIOLOGY:

Hemorrhoid disease is a common disease in Malaysia. However, there are no exact figures of the incidence and prevalence rate of hemorrhoid disease in Malaysia, most probably due to "shy" nature of Malaysians that refuse to seek for medical treatment. Factors that increase intra-abdominal pressure (e.g., prolonged straining, constipation, pregnancy, ascites) contribute to dilatation, engorgement, and prolapsed of hemorrhoidal vascular tissue.[1,2]

DEFINITION:

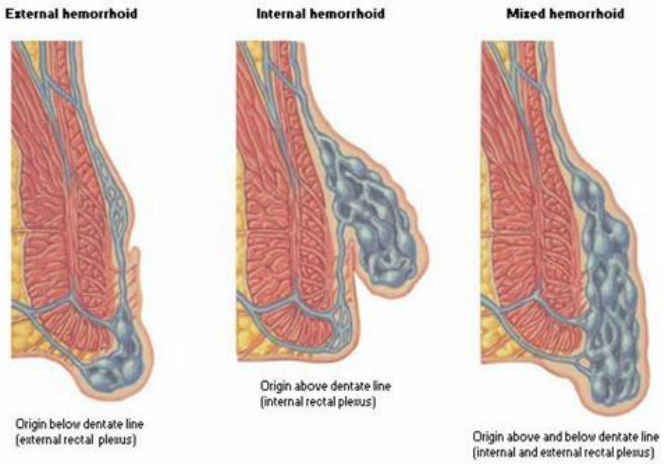
Hemorrhoid is defined as abnormal enlargement of anal cushions containing arteriovenous anastomosis, conventionally described as occurring in the 3, 7 and 11 o'clock positions. The vascular supply is from branches of the superior rectal artery, which are drained by veins (internal venous plexus), emptying into the superior rectal vein. Internal hemorrhoids, which originate from above the dentate line of the anal canal, occur when these anal cushions are dragged down the canal.[3,4]

HISTORY:

The word "hemorrhoid' came from the ancient Greek word "haema" (blood) and "rhoos" (flow), in which the meaning of the word is the flow of blood. It is assumed that, the first person to use the term "hemorrhoid" was Hippocrates (460BC). Hemorrhoid is also known as "pile", which derives from the Latin word *pila* (ball), which means swelling anal (round mass). The term "piles" are generally being used since 1307 AD by English doctor named John of Arderne.[1]

PATHOPHYSIOLOGY:

Elevated pressure in the hemorrhoidal plexus causes dilation of venous plexuses. Elevations of intraabdominal pressure causes dilation of vascular, and if persistent may lead to formation of hemorrhoid. Older patients tend to have hemorrhoids, as one of the risk factors of hemorrhoids is degradation of normal supporting structures in the hemorrhoidal plexus[6].



SIGN AND SYMPTOMS:

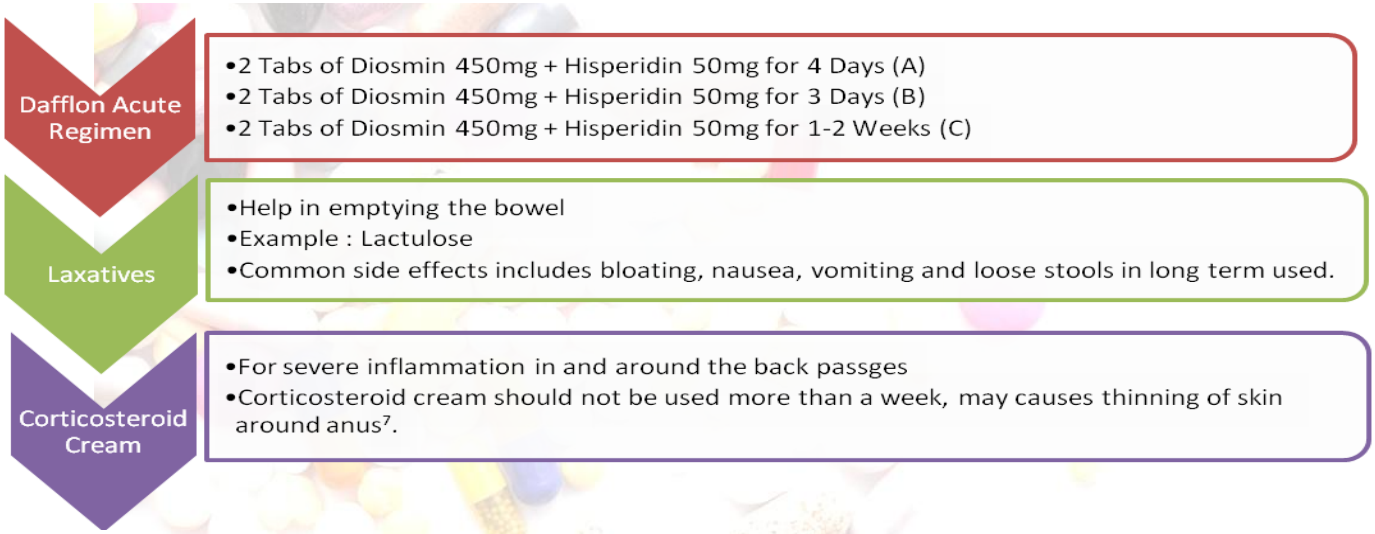
Both internal and external hemorrhoids may cause anal discharges and itching. Internal hemorrhoids typically cause prolapsed or painless rectal bleeding, which are usually being reported as having blood stains on toilet papers or bleeding after each bowel movement. External hemorrhoids may lead to anal discomfort, partly due to the engorgement. Worsening of the symptoms may occur if patients choose to treat hemorrhoids without any medical advices.[2]

Types of Hemorrhoids[3,4,5]	Descriptions

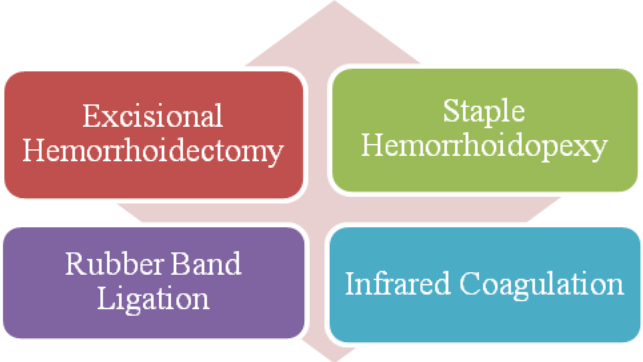
Internal	• Internal hemorrhoids grow from within the rectum that's above the pectinate line. Internal hemorrhoids are encased in a lining called mucosa that is not sensitive to touch, pain, stretching or temperature.
	• There are 4 Grades of internal hemorrhoids[3]
	  • Grade I- not protruding into the anal canal but may cause bleeding
	  • Grade II- spontaneously move back inside the canal when protruding
	  • Grade III- can be pushed back inside the anal canal using finger when prolapsed outside the canal
	  • Grade IV- prolapsed outside the canal permanently.

External	• Originate below the dentate line and with thrombosis, acute pain may be experienced. • May cause perianal itch and excoriation, due to difficulty with perianal hygiene[5].

PHARMACOLOGICAL TREATMENT OF HEMORRHOIDS[7]:



NON-PHARMACOLOGICAL TREATMENT OF HEMORRHOIDS



CONCLUSION:

Hemorrhoid is a disease where anal cushion is enlarged. Pain may be experienced, but not in all the cases. Hemorrhoid is common, but it is advised to not taken lightly of, and to seek for medical advices. The management of hemorrhoids depends on the severity of hemorrhoids.

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LEPROSY

By: **LEE AI LENG**

Leprosy, also known as Hansen's disease, is an infection caused by slow-growing bacteria called *Mycobacterium leprae*, an acid-fast, rod-shaped bacillus.[1] Hansen's disease was first described in ancient Indian back in 6th Century BC. Leprosy is a chronic non-fatal infectious disease, which affect mainly the cooler parts of the body such as the skin, mouth, respiratory tract, eyes, peripheral nerves, superficial lymph nodes and testis.[2]

Mycobacterium leprae resembles closely to *Mycobacterium tuberculosis* but is less acid-fast. It grows very slowly and may take up to 20 years to develop signs of infection.[3] Although the earliest and main involvement sites of leprosy are the skin and nerves, other organs such as liver, spleen, bone marrow and regional lymph nodes may also be involved, due to bacteraemia from endothelial colonisation or by bacilli filtered from blood by the reticuloendothelial system.[2] In advanced cases, secondary amyloidosis and renal disease, which are immunologic in origin, may be developed.

Leprosy is a slow communicable disease, with incubation period between the first exposure and the appearance of signs of disease that varies from 2 to 20 years.[2] Prolonged close contact with someone with untreated leprosy patients, who shed numerous bacilli from damaged skin, nasal secretions, mucous membrane of mouth and hair follicle, may catch the disease.[1] Similar with tuberculosis, the immune response in leprosy is also due to T cell-mediated delayed hypersensitivity. However, these two diseases are quite different in terms of the immune reactions and lesions. *Mycobacterium leprae* does not produce any toxins but the damage to tissues is immune-mediated.[2]

Leprosy is broadly classified into 2 main types; lepromatous type and tuberculoid type. Both of these types of leprosy represent two opposite poles of host immune response, which are also called polar forms of leprosy.[2] The pathogenesis for both types of leprosy are as shown in Figure 1.

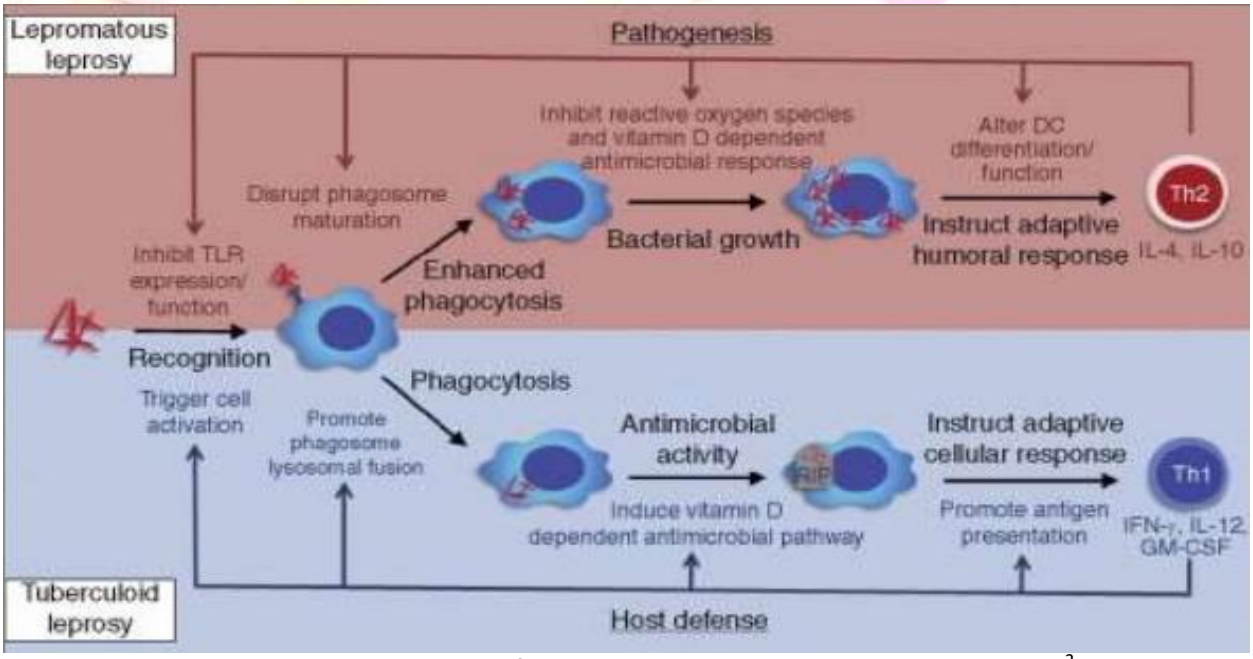


Figure 1: Pathogenesis of Lepromatous leprosy and Tuberculoid leprosy[2]

Skin lesions in lepromatous leprosy are generally symmetrical, multiple, slightly hypo-pigmented and erythematous macules, papules, nodules or diffuse infiltrates. The nodular lesions may coalesce to give leonine facies appearance. The lesions are hypoaesthetic or anaesthetic but sensory disturbance is less compared to

tuberculoid leprosy. The skin lesions in tuberculoid leprosy occur as either single or as a few asymmetrical lesions which are hypo-pigmented and erythematous macules. Distinct sensory impairment in tuberculoid leprosy are often present.[1,2] The differences between the both types of leprosy are shown in Table 1.

Lepromatous leprosy	Tuberculoid leprosy
Extensively spread all over the body	Restricted pathogenic growth
Most severe stage of leprosy	Less severe case of leprosy
Poor cell-mediated immunity	High cell-mediated immunity
Involves a relatively higher bacterial load	Does not involve a higher amount of bacterial load

Table 1: Differences between Lepromatous leprosy and Tuberculoid leprosy[2]

Symptoms of leprosy mainly affect the skin, nerves and mucous membranes. The disease may cause skin symptoms such as discoloured patches of skin which usually are flat that may be numb and faded-looking, nodules on the skin, thick, stiff or dry skin, painless ulcers on the soles of feet, painless swelling or lumps on the face or earlobes and loss of eyebrows or eyelashes. Symptoms caused by damage to the nerves are numbness of affected areas of the skin, muscle weakness or paralysis, enlarged nerves and eye problems that may lead to blindness. Symptoms caused by the disease in the mucous membranes are stuffy nose and nosebleeds.[1]

Leprosy is curable and treatment in the early stages can prevent disability. Multidrug treatment is available and it provides a highly effective cure for all types of leprosy.[3] Multidrug therapy includes Dapsone with Rifampicin and Clofazimine. These combination of antibiotics helps to prevent development of antibiotic resistance. Treatment usually lasts between one to two years. Leprosy is curable if the treatment is completed as prescribed.[1] The multidrug treatments recommended by WHO are shown in Table 2. The antibiotics used during the treatment will kill the bacteria, which may cure the disease and prevent it from deteriorating, but they do not reverse the nerve damage or physical disfiguration that may have occurred before the diagnosis[1,2,3]

Type of leprosy	Regimen		Duration of treatment
	Monthly Supervised	Daily Self Administered	
Paucibacillary	Rifampicin, 600mg	Dapsone, 100mg	6 months
Multibacillary	Rifampicin, 600mg Clofazimine, 300mg	Clofazimine, 50mg Dapsone, 100mg	12 months
Patients with high bacterial load may need treatment for at least 25 months.			

Table 2: WHO recommendation of multidrug regimens for leprosy [3]

The nerve damage can result in paralysis and crippling of hands and feet. In very advanced cases, the person may have multiple injuries due to lack of sensation, and eventually the body may reabsorb the affected digits over time, resulting in the apparent loss of toes and fingers. Corneal ulcers or blindness can also occur if facial nerves are affected.[1,2]

Leprosy may be dangerous if left untreated. Thus, it is very important for early diagnosis of disease before any permanent nerve damage occurs.[1]

References

1. Hansen's Disease (Leprosy). 2017. Centers for Disease Control and Prevention (CDC).
2. Harsh Mohan. (2010). Textbook of Pathology, 6th Edition, Jaypee: 157-161.
3. Leprosy (2017). World Health Organization (WHO).

Medication Error Reporting

By: **GOH JUN XIAN, JOEL**

CASE #1 (SUPPLY OF INAPPROPRIATE PHARMACEUTICAL PRODUCT)

Event summary	Recommended remedial actions
On the 29th of March 2017, a premature infant of 27 weeks at birth, weighing 0.9 kg, was initiated on total parenteral nutrition (TPN) as a source of nutrient due to presumed sepsis. The doctor had ordered a nutrient bag without additional electrolytes for this particular patient. However, the pharmacist on duty supplied a nutrient bag containing additional sodium and potassium, despite clear writing indicating that the bag had additional electrolytes. Moreover, the bag was not counter-checked prior to supply. 12 hours after the bag was supplied, the patient developed a bout of hyperkalemia, which was incidentally detected when the patient's renal function was monitored. The error was traced to the nutrient bag and it was subsequently replaced. The patient's serum potassium level was restored the following day.	1. As there is no allocated physical space for unused TPN bags, improving quarantine procedures for these bags is recommended. **A space should be designated** in the refrigerator for unused bags with a **quarantine label** attached. 2. **Counter-checking** and signature by a senior pharmacist before supply of TPN bags. 3. **Additional labels** to indicate additives on the bags for ease of identification. 4. As staff members may not be fully informed on the status of the bags, improving interpersonal **communication** is imperative.

CASE #2 (WRONG SUPPLY OF MEDICATION)

Event summary	Recommended remedial actions
On the 14th of April 2017, a 43-year old female patient, diagnosed with bipolar disorder was prescribed T. Zolpidem 20mg ON to aid in sleep. However, T. Diazepam 5mg was filled and dispensed to the patient instead of T. Zolpidem 10mg. The patient returned to the pharmacy on the 17th of April 2017 due to complaints of not being able to sleep despite taking a total of 4 tablets of her sleeping pills the previous night. She claimed that she was usually able to sleep after taking her usual dose of 2 tablets of zolpidem and 1 tablet of clonazepam (2mg). The error was then detected and the medications were returned and replaced. Upon investigation by the doctor via telephone, the patient's husband claimed that she did not exhibit any signs of toxicity.	1. **Verbalise** the medications during counter-checking. 2. **Double-check the medications during dispensing**, especially when the patient inquires of the medications. 3. **Properly brief new staffs** on Dangerous Drug (DD) handling procedures, and for staffs to immediately **report to pharmacist in-charge** if inconsistencies arise during book-keeping. 4. **Rearrange** the DDs systematically. 5. Pharmacist in-charge should **supervise** Provisionally Registered Pharmacists (PRP) during handling of DDs and to counter-check with aforementioned PRP. 6. **DD training** should be adopted as a component of the orientation kit.

The above excerpts were extracted from the Root Cause Analysis (RCA) Meeting (Bil. 5/2017) by the Medication Safety and Risk Management Committee of Hospital Putrajaya.

ADVERSE DRUG REACTION (ADR) REPORTS

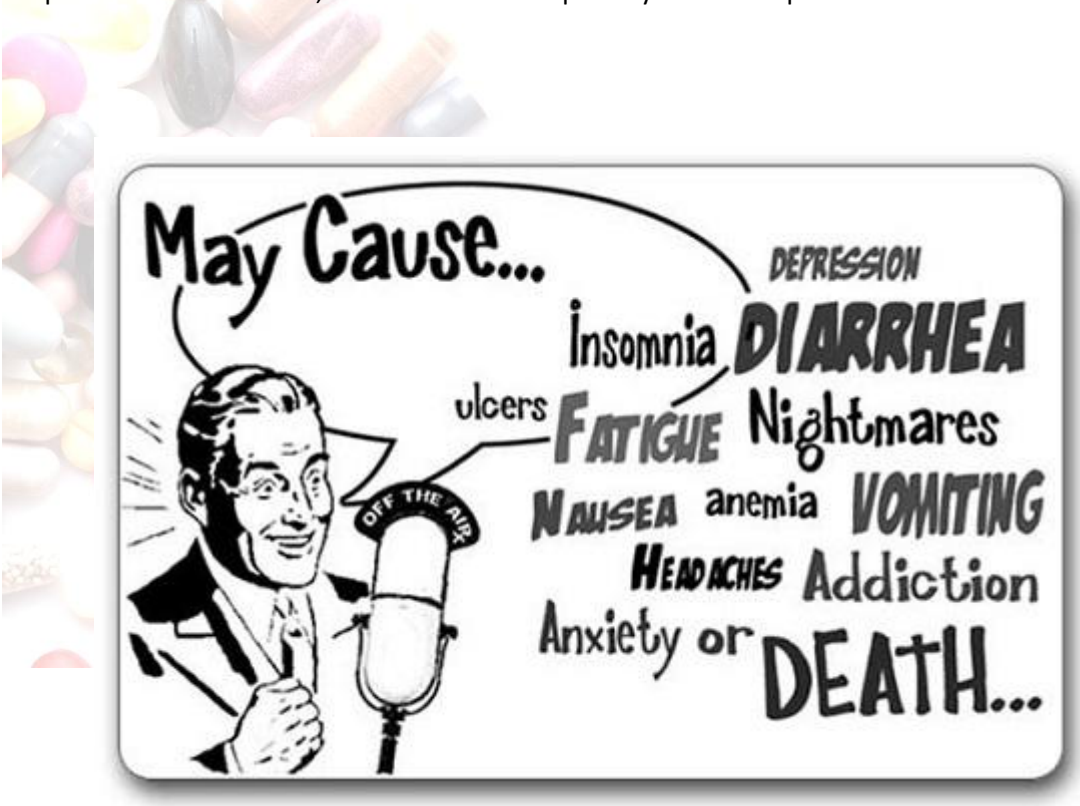
By: **NADIAH MOHAMED KHAZIN**

CASE 1 – Vasculitis Lesion suspected due to intake of Health Supplements

37 year old Malay lady was referred to Dermatology Department in December 2016 from Emergency Department due to vasculitis Lesion over bilateral hands and feet, suspected due to Hydroxycut Advanced and Kitsui Generation 2 Collagen. She was then prescribed with Tablet Prednisolone, Aqueous cream and Bethamethasone 1% cream. An ADR report with samples of the products was submitted to National Centre for Adverse Drug Reactions Monitoring, National Pharmaceutical Regulatory Agency (NPRA).

Feedback from NPRA:

Upon investigation, it was found that Kitsui Generation 2 Collagen was not registered with Drug Control Authority, thus this case was forwarded to Department of Pharmacy Enforcement, Ministry of Health. Furthermore, analysis of the samples could not be done, due to insufficient quantity of the sample submitted.



Case 3 – Hyperpigmented patch over cheeks after 3 months use of Khadija Cream and Nutrafemme.

In early September 2016, a patient started using a range of cosmetic products by Khadija (switching from other brand of cosmetic products). At the same time, patient also took Nutrafemme as anti-aging supplement. After three months, she developed hyperpigmentation over the cheeks; hence she was adviced to stop the products. An ADR report was submitted with samples of the suspected products to National Centre for Adverse Drug Reactions Monitoring, National Pharmaceutical Regulatory Agency (NPRA).

Pictures of the suspected cosmetic products submitted

Feedback from NPRA:

The samples of the products were analysed and the results were as follow:

No.	Product Name	Results
1.	Khadija Day Cream	• Negative results on hydroquinone, tretinoin and arbutin • Do not exceed the permitted limits of mercury and plumbum
2.	Khadija Whitening Night Cream	• Suspected positive, product was adulterated with hydroquinone (confirmatory test was unable to be done due to insufficient quantity of sample)
3.	Khadija Flawless Night Cream	• Negative results on hydroquinone and arbutin
4.	Nutrafemme	• Analysis of the samples could not be done due to insufficient quantity of the sample

Upon investigation the NPRA notification for the Khadija range of cosmetics involved in this ADR were expired on 13th February 2017. Thus, this report was forwarded to Department of Pharmacy Enforcement, Ministry of Health. However, the Nutrafemme is not considered as 'Controlled Drug', therefore the issue was being forwarded to Food Safety and Quality Program of the Ministry of Health Malaysia for further investigation.

The above excerpts were extracted from ADR case reports submitted to Drug Information Services, Pharmacy Department

LABORATORY TESTING FOR SUSPECTED ADULTERATED PRODUCTS

By: **NADIAH MOHAMED KHAZIN**

Adulterated is defined as to corrupt, debase, or make impure by the addition of a foreign or inferior substance or element; especially: to prepare for sale by replacing more valuable with less valuable or inert ingredients. In Malaysia, adulterated products continued to be identified, not only traditional products, but also medicinal products. The common adulterated products are dexamethasone, prednisolone, sildenafil, tadalafil, chlorpheniramine and sibutramine.

One of the services provided by National Pharmaceutical Regulatory Agency (NPRA) is to run laboratory testing for suspected adulterated products. Below is the information required for laboratory testing to be conducted, when ADR occurs and adulteration is suspected:

1. Fill in the adverse drug reaction (ADR) reporting form for healthcare professionals (or Consumer Medications Complaints reporting form- for consumers who wish to report directly to the NPCB). Please include as many details as possible to ensure the report is useful.

   Important details:
   - Name and contact details of patient
   - Details of the ADR
   - Details of any concomitant medicines/ other products taken and underlying illnesses
   - Product name and label
   - Where it was obtained
   - Indication for which the patient was taking the product
   - Suspected adulterant (e.g. antihistamine, steroid) based on product indication and ADR
   - Name and contact details of reporter

2. Submit the ADR form together with the product sample. Preferably samples should be sent in the original packaging or at least with clear pictures of the product from all angles. Please send as much sample quantity as possible. The quantities listed below are for the screening of one suspected adulterant only. Therefore, the quantity should be multiplied based on the number of suspected adulterants.

Minimum sample quantity required for laboratory testing for adulterant

Dosage Form	Minimum amount for one test	Total amount for confirmatory result
Tablet/ Capsule/ Pill	10g or 20 dosage forms	30g or 60 dosage forms
Liquid	40ml/40g	120ml / 120g
Powder	10g	30g
Cream	10g	30g
Candy	10 candles	30 candles

References:

1. https://www.merriam-webster.com/dictionary/adulterate
2. NPCB: ADR Reported Guide