DRUG NEWSLETTER

Unit Farmasi Klinikal Dan Maklumat Drug
Jabatan Farmasi
Hospital Pakar USM

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HYPERTENSION IN PREGNANCY

Introduction

Hypertension is one of the most common medical disorders during pregnancy and a major cause of **maternal and perinatal morbidity and mortality**. It affects approximately 5–10% of pregnancies.[1] **Early recognition and proper treatment are crucial** to prevent complications such as preeclampsia, eclampsia, placental abruption and fetal growth restriction.[1,3]

What's Interesting?

Classification of Hypertensive Disorders in Pregnancy[1,2]

TYPE	DEFINITION	TIMING / NOTES
Chronic Hypertension	BP ≥140/90 mmHg **before 20 weeks** of gestation or pre-existing	May persist postpartum
Gestational Hypertension	BP ≥140/90 mmHg **after 20 weeks**, no proteinuria	Usually resolves postpartum
Preeclampsia (PE)	Hypertension **after 20 weeks** + **proteinuria (≥300 mg/24h)** or end-organ dysfunction	Can progress to eclampsia
Eclampsia	Preeclampsia + **seizures**	Obstetric emergency
Chronic Hypertension with Superimposed Preeclampsia	Pre-existing HTN with new-onset proteinuria or worsening control	Higher risk of complications

[iStock photo]

Recognition of Women at Risk of Preeclampsia for Commencement of Prophylaxis[3]

Moderate risk:

- primigravida (first pregnancy)
- age >40 years
- pregnancy interval >10 years
- body mass index of >35 kg/m2 at first visit
- family history of PE
- multiple pregnancy

High risk:

- hypertensive disease during previous pregnancy
- chronic kidney disease
- autoimmune disease such as Systemic Lupus Erythematosus (SLE) or anti-phospholipid syndrome (APS)
- type 1 or type 2 diabetes mellitus
- chronic hypertension

Preeclampsia (PE) Prophylactic Therapy[3]

A) ASPIRIN

- Women with ≥2 moderate or one high risk factor should be started on low dose aspirin **from 12 weeks up to 16 weeks of gestation until delivery.**
- Dose: 100-150mg at bedtime in order to significantly reduce the incidence of PE.

B) CALCIUM

- Low dose calcium supplement (generally 500-1000mg elemental calcium daily) commenced **before 20 weeks gestation** reduces the risk of PE.

Anti-Hypertensive Drugs Commonly Used in Pregnancy[3]

DRUG	REMARKS
Methyldopa (first line)	Oral 250mg TDS, doubling every 48 hrs (up to 1gm TDS) until BP well controlled. Oldest antihypertensive agent used in pregnancy, with best safety profile.
Labetalol (alternative first line)	Oral 100mg BD, doubling every 48 hrs (up to 400mg BD) until BP well controlled.
Nifedipine (second line)	Oral 10mg TDS, up to 20mg TDS, when BP poorly controlled despite maximum doses of methyldopa ± labetalol.

Anti-Hypertensive Drugs for Severe Preeclampsia with Acute Hypertensive Crisis[3]

Severe preeclampsia should be recognized early for urgent hospital admission and monitoring to ensure **timely delivery**.

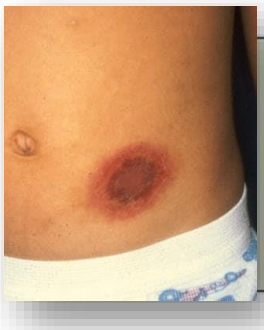
DRUG	ADMINISTRATION	REMARKS
Labetalol	**In IV bolus:** • 20 mg then 40 mg 10–20 mins later • 80 mg every 10–15 mins up to 200 mg **Infusion:** continuous infusion of 1–2 mg/min until BP stabilises, then stop or reduce to 0.5 mg/min.	May cause fetal bradycardia.
Nifedipine	**Oral** 5–10 mg stat (repeat in 30 mins if necessary). After the initial emergency dose, 10–20 mg can be given every 3–6 hrs until BP stabilises.	Especially prior to transferring a patient from a peripheral clinic to hospital.

References:
1. NICE Guideline NG133: *Hypertension in Pregnancy: Diagnosis and Management* (2023)
2. ACOG Practice Bulletin No. 222: *Gestational Hypertension and Preeclampsia* (2020)
3. Ministry of Health Malaysia: CPG Management of Hypertension, 5th edition (2018)

Doxycycline-Fixed Drug Eruption (FDE)

OVERVIEW

- Doxycycline is a broad-spectrum antibiotic effective against a wide variety of gram-positive and gram-negative microorganisms.
- It acts mainly as a bacteriostatic agent and is believed to exert its antimicrobial activity by inhibiting protein synthesis.



Fixed drug eruption (FDE)

- A common drug-induced skin reaction characterized by the recurrence of lesions at the same sites upon re-exposure to the offending medication.
- It represents a delayed type IV hypersensitivity reaction mediated by memory CD8+ T cells residing in the skin.

This signal originated from India's Central Drugs Standard Control Organization (CDSCO), as reported in the *WHO Pharmaceuticals Newsletter No. 3, 2022*. The CDSCO approved an update to the doxycycline prescribing information to include fixed drug eruption as an adverse reaction. The National Coordination Centre – Pharmacovigilance Programme of India reviewed 94 cases and confirmed a strong causal link between doxycycline and the event.

Following the review, the NPRA issued Directive [NPRA.600-1/9/13 (65) Jld 1], instructing all product registration holders of **doxycycline-containing products** to update the local package inserts and Consumer Medication Information Leaflets (RiMUPs) to incorporate information on the risk of **fixed drug eruption (FDE)**.

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Selangor
MALAYSIA

Ruj. Kami : NPRA.600-1/9/13 (65) Jld.1
Tarikh : 15 Ogos 2025

SEMUA PEMEGANG PENDAFTARAN PRODUK

SEMUA PERSATUAN BERKENAAN
(SEPERTI DI SENARAI EDARAN)

Tuan / Puan,

PERATURAN-PERATURAN KAWALAN DADAH DAN KOSMETIK 1984 ARAHAN PENGARAH PERKHIDMATAN FARMASI BILANGAN 18 TAHUN 2025 DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI DOXYCYCLINE: PENGEMASKINIAN SISIP BUNGKUSAN DAN RISALAH MAKLUMAT UBAT UNTUK PENGGUNA (RiMUP) DENGAN MAKLUMAT KESELAMATAN BERKAITAN RISIKO FIXED ERUPTION (FE)/ FIXED DRUG ERUPTION (FDE)

Dengan hormatnya saya merujuk kepada perkara di atas.

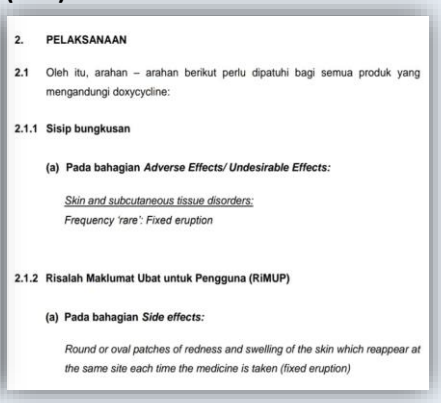
2. Dikemukakan Arahan Pengarah Perkhidmatan Farmasi Bilangan 18 Tahun 2025, Direktif untuk semua produk yang mengandungi doxycycline : Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko *Fixed Eruption (FE)/ Fixed Drug Eruption (FDE)* untuk makluman dan perhatian tuan/puan. Tuan/Puan adalah diarahkan untuk mematuhi keperluan tersebut.

Sekian, terima kasih.

"MALAYSIA MADANI"

"BERKHIDMAT UNTUK NEGARA"

Saya yang menjalankan amanah



2. PELAKSANAAN

2.1 Oleh itu, arahan – arahan berikut perlu dipatuhi bagi semua produk yang mengandungi doxycycline:

2.1.1 Sisip bungkusan

(a) Pada bahagian *Adverse Effects/ Undesirable Effects:*

Skin and subcutaneous tissue disorders:
Frequency 'rare': Fixed eruption

2.1.2 Risalah Maklumat Ubat untuk Pengguna (RiMUP)

(a) Pada bahagian *Side effects:*

Round or oval patches of redness and swelling of the skin which reappear at the same site each time the medicine is taken (fixed eruption)

RECOMMENDATIONS

- Be aware that skin reactions, including fixed drug eruptions, have been reported with doxycycline use.
- Patients should promptly inform their doctor if round or oval red, swollen skin patches reappear at the same site after taking doxycycline.
- All suspected adverse reactions related to doxycycline-containing products should be reported to the NPRA.

References:

1. Hariraj, V. (2025, October 13). *Safety Signal Alert: Doxycycline-fixed drug eruption (FDE)*. National Pharmaceutical Regulatory Agency (NPRA). https://www.npra.gov.my/index.php/en/industry-news-announcements/more-recent-updates/465-english/safety-alerts-main/safety-alerts-2025/1527775-safety-signal-alert-doxycycline-fixed-drug-eruption-fde.html
2. Arahan Pengarah Perkhidmatan Farmasi Bilangan 18 Tahun 2025, Bahagian Regulatori Farmasi Negara (NPRA)

Valproate (Sodium Valproate, Valproic Acid):
Potential Risks to Offspring Following Paternal Exposure, and Male Infertility

OVERVIEW

Valproate (as sodium valproate or valproic acid) is approved in Malaysia to treat epilepsy and mania associated with bipolar disorder. The most likely mechanism of action involves potentiation of gamma amino-butyric acid (GABA) inhibitory effects through modulation of GABA synthesis or metabolism.

SAFETY ISSUES

① ***Potential risk of neurodevelopmental disorders (NDDs) due to paternal exposure prior to conception***

The retrospective observational study, suggests a potential increased risk of NDDs in children born to men taking valproate in the 3 months before conception, compared to those treated with lamotrigine or levetiracetam.

② ***Potential risk of transgenerational epigenetic inheritance following paternal exposure to valproate***

In mice, paternal valproate exposure has been linked to behavioural changes across first to third generations, including autism-like traits

③ ***Risk of male infertility***

Reported effects include reduced free testosterone and follicle-stimulating hormone (FSH) levels, lower sperm count and motility, abnormal sperm morphology, and decreased testicular volume.

ADVICE FOR HEALTHCARE PROFESSIONALS

- ✓ Be aware of emerging evidence suggesting a **potential risk of NDD, including autism spectrum disorders (ASD)**, in children born to fathers treated with valproate during the 3 months prior to conception.
- ✓ Advise on the **need for effective contraception (including for the female partner) and to avoid sperm donation** during treatment and for at least 3 months after discontinuation.
- ✓ Educate those planning to father a child to **consult their doctor about alternative treatment options**.
- ✓ Remind on **the importance of reporting any sexual dysfunction or fertility concerns while on valproate.**
- ✓ **Emphasise on adherence** that patients should not stop valproate treatment abruptly without medical advice, as this could worsen their underlying condition.

References;

1. Noor'ain S, Choo Sim Mei et al. (2025, August 19). Valproate (Sodium Valproate, Valproic Acid): Potential Risks to Offspring Following Paternal Exposure, and Male Infertility. National Pharmaceutical Regulatory Agency (NPRA) - Home. https://www.npra.gov.my/index.php/en/component/content/article/465-english/safety-alerts-main/safety-alerts-2025/1527743-valproate
2. National Pharmaceutical Regulatory Agency (NPRA). EPILIM (sodium valproate) [Package Insert]. QUEST3+ Product Search. 2025 June [cited 2025 Jun 30]. Available from: https://www.npra.gov.my

Suggestion and comments

Let us know what you think by reaching us at:
https://pharmacy.kk.usm.my/index.php?view=article&id=146&catid=22

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