APRIL 2014

MADRAC

Malaysian Adverse Drug Reactions Newsletter
National Pharmaceutical Control Bureau, Ministry of Health Malaysia
This newsletter is also available on our website: http://www.bpfk.gov.my

SAFETY ISSUES OF CURRENT INTEREST

INDIVIDUAL GENETIC MAKE-UP, A KEY TO PERSONALISED MEDICINE
by Norleen Mohamed Ali

Background

Genetic polymorphism is a term used to describe a gene variation which exists at a frequency of more than 1% in a population. The existence of polymorphism may lead to differences in drug efficacy and toxicity between individuals[1]. The study of how genetic polymorphism relates to variation in drug responses has given rise to the field of **pharmacogenetics**[2].

Pharmacogenomics refers to the study of genes which affect drug behaviour in the body. This knowledge allows drug selection to be customised according to a patient's genetic makeup. Currently, drugs are prescribed to meet the needs of the general population. However, variations in genetic profile can render them ineffective or result in serious adverse effects (***Figure 1*** *overleaf*).

The DNA variations known as single nucleotide polymorphisms, or SNPs (*pronounced "snips"*), are caused by substitution of one of the four chemical bases – adenine (A), thymine (T), guanine (G) or cytosine (C). This substitution may lead to protein changes that predispose to disease or alter the ability to metabolise drugs[3].

C O N T E N T

To report an adverse drug reaction:

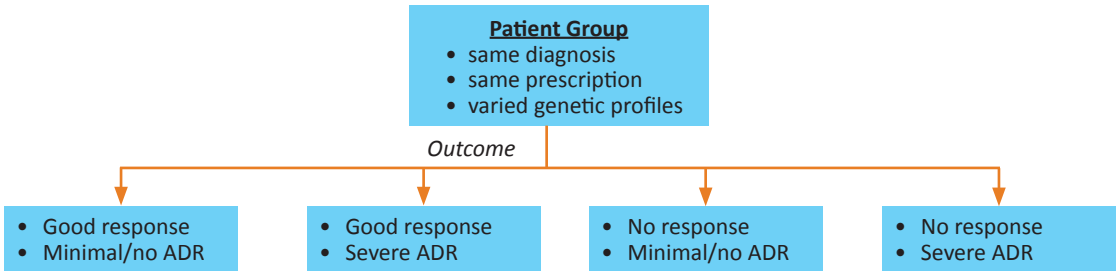
1. Visit http://www.bpfk.gov.my
2. Click on the red box: 'Reporting Medicinal Problems'.
3. Go to report as a healthcare professional online or via hardcopy.
4. Submit the form once completed.

Alternatively, please contact:

The Drug Safety Monitoring Centre,
National Pharmaceutical Control Bureau,
Ministry of Health
PO Box 319, Jalan Sultan,
46730 Petaling Jaya,
Selangor.

Tel : +603 78835550
Fax : +603 79567151

Figure 1: Effect of genetic profile variation on therapeutic response



Genetic polymorphisms affecting drug response

Both the cytochrome P-450 (CYP450) enzymes and human leukocyte antigens (HLA) are affected by SNPs. These variations can affect the drug metabolising ability of individuals (***Table 1***)[3-6]. Patients may be divided into four metaboliser categories according to the activity level of CYP enzymes, namely poor, intermediate, extensive, and ultrarapid metabolisers. If the enzymes are less active than usual, drugs may stay within the body for too long causing overdose. Enzymes that are more efficient than normal can eliminate a drug too quickly, which reduces drug efficacy.

Table 1: Examples of gene variants affecting clinical effect of drugs

Gene variant	Affected Drugs	Clinical or Adverse Effect
CYP1A2	Antipsychotics	Increase toxicity, reduce effectiveness
CYP2D6	Antidepressants, β-blockers	Increase toxicity, reduce effectiveness
CYP2D6	Codeine	Decrease analgesic effect
CYP2C9	Warfarin	Increase anticoagulant effect
VKORC1	Warfarin	Reduce anticoagulant effect
APOE	HMG-CoA reductase inhibitors	Statin effectiveness
UGT1A1	Irinotecan	Severe/fatal neutropenia
TPMT	Azathioprine	Azathioprine toxicity
KRAS	Cetuximab, Panitumumab	Drug resistance
HLA Variants:		
HLA-B*5701	Abacavir	Increase hypersensitivity
HLA-A29, HLA-B12, HLA-DR7	Sulfonamides	Stevens-Johnson syndrome (SJS)
HLA-A2 and HLA-B12	Oxicam	SJS/ Toxic epidermal necrolysis
HLA-B*1502	Carbamazepine	Severe cutaneous reactions
HLA-B*5801	Allopurinol	Severe cutaneous reactions

Key:
CYP: *Cytochrome P;* ***VKORC:*** *Vitamin K Epoxide Reductase Complex;* ***HLA:*** *Human Leukocyte Antigen;* ***APOE:*** *Alipoprotein E;* ***UGT:*** *UDP-glucunorosyltransferase;* ***TPMT:*** *thiopurine methyltransferase;* ***KRAS:*** *Kirsten rat sarcoma viral oncogene homolog*

Pharmacogenetic testing

Pharmacogenetic testing is carried out in certain countries for specific drugs, such as warfarin, carbamazepine, and psychotropics[3]. These tests allow patients to be screened for potentially poor responses to drugs or increased susceptibility to adverse effects. In Malaysia, a pharmacogenetic testing kit has been developed for HLA-B*1502 which may act as a gene-marker for carbamazepine-induced SJS. Discussions are underway to establish routine testing prior to starting carbamazepine in new patients.

Conclusion

Understanding genetic contributors to drug response variability allows healthcare providers to look for unexpected toxicities and predict which patients are more likely to respond optimally to a prescribed medication. The ability to provide a patient with a predictable response and minimal risk of ADR will increase patient compliance and improve cost effectiveness[2].

References :

1. Brazell C, Freeman A & Mosteller M (2002). *Maximizing the Value of Medicines by Including Pharmacogenetic Research in Drug Development and Surveillance.* Br J Clin Pharmacol. 53(3): 224 -231.
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5. Pirmohamed M (2006). *Genetic Factors in the Predisposition to Drug-induced Hypersensitivity Reactions.* AAPS Journal. 8(1): E20-E26.
6. Chung W, Hung S & Chen Y (2007). *Human Leukocyte Antigens and Drug Hypersensitivity.* Current Opinion in Allergy and Clinical Immunology. 7(4): 317-323.

HUMAN PAPILLOMAVIRUS (HPV) VACCINE: COMPLEX REGIONAL PAIN SYNDROME (CRPS)

by Ng Chiew Seng and Noraisyah Mohd. Sani

About HPV Vaccination

The World Health Organisation (WHO) recommends the introduction of human papillomavirus (HPV) vaccination into national immunisation programmes where cervical cancer prevention is a public health priority and it is programmatically feasible. The Malaysian HPV Immunisation Programme was launched in September 2010, targeting teenage girls aged 13 years. A catch-up programme for women aged 18 years was launched in July 2012 under the National Population and Family Development Board (LPPKN). There are currently two (2) HPV vaccines registered in Malaysia: Cervarix® (containing HPV types 16 & 18) and Gardasil® (containing HPV types 6, 11, 16 & 18).

Background of safety issue

In June 2013, the Japanese Ministry of Health, Labor and Welfare (MHLW) suspended active recommendation of HPV vaccination after almost 2,000 adverse reactions to the HPV vaccines were reported within three years, including long-term pain and numbness[1]. Several cases of complex regional pain syndrome (CRPS) have been highlighted in Japan, where more than 8 million doses of HPV vaccine have been distributed. Although no regulatory action was taken against the HPV vaccine license holders, the MHLW instructed local governments not to promote the use of the vaccines while further studies were being conducted on the adverse events, particularly CRPS.

In January 2014, the MHLW Vaccines Safety Committee announced that the chronic pain appeared to be psychosomatic in nature (i.e. anxiety due to vaccination). An expert advisory committee continues to review the situation and has yet to conclude whether to return to proactive recommendation of HPV vaccination.

Complex Regional Pain Syndrome (CRPS)

CRPS is a chronic pain most often affecting one of the limbs, usually after an injury or trauma to that limb. It can affect both men and women. Children do not get it before age five and only very rarely before age ten, but it is not uncommon in teenagers[2]. The WHO ADR database contains 52 cases of CRPS related to HPV vaccination reported between 2009 and 2014*. Thirteen (13) of these reports were submitted from Japan.

The key symptom of CRPS is prolonged pain. The pain may feel like a burning or “pins and needles” sensation. It may spread to the entire limb or travel to the opposite extremity. People with CRPS also experience constant or intermittent changes in temperature, skin color, and swelling of the affected limb due to abnormal microcirculation. This is caused by damage to the nerves controlling blood flow and temperature. The exact pathogenesis of CRPS is still unclear. In more than 90% of cases, the condition is triggered by a clear history of trauma or injury. Limited data suggest that CRPS also may be influenced by genetics. The outcome of CRPS varies from person to person. Almost all children and teenagers have good recovery.

***Disclaimer:** This information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases. This information does not represent the opinion of WHO.*

Local Scenario

Since the launch of the National HPV Immunisation Programme in 2010 until the end of 2013, a total of 6,867 adverse events following immunisation (AEFI) reports have been received by the Drug Safety Monitoring Centre through the active surveillance program. The majority of these reactions were of mild to moderate severity, not long-lasting, and were documented in the package inserts. Frequently reported reactions include injection site pain, swelling, erythema, and generalised weakness. None of the reports related to **prolonged** injection site pain or body ache post-HPV vaccination.

CRPS is classified by the WHO as an autonomic nervous system disorder. To date, no CRPS or other adverse event related to autonomic nervous system disorders have been reported in Malaysia post-HPV vaccination. CRPS-associated symptoms such as muscle ache (87 reports), body aching (588) and limb weakness (480) have been reported but were mostly mild in nature and the patients subsequently recovered.

Conclusion

It is plausible that CRPS could develop following the injection of any vaccine. However, to date, the WHO Global Advisory Committee on Vaccine Safety (GACVS) has not found any safety issue that would alter the current recommendations for the use of HPV vaccines[5,6]. The NPCB will continue to monitor this issue closely.

Healthcare professionals are advised to report any suspected adverse events related to HPV vaccination to NPCB. Besides that, patients and their parents should be educated on the benefits of HPV vaccination in cervical cancer prevention as well as possible rare adverse events such as anaphylaxis. Healthcare providers in the **private sector** are advised to distribute the simplified AEFI reporting form to patients or their parents after HPV vaccination, as is done in the government setting. Please remind patients to seek medical attention and submit the form if any adverse reactions occur. The simplified AEFI form can be downloaded from the NPCB website: (http://portal.bpfk.gov.my/aeimages//File/Borang_AEFI_ringan_pindaan_3_2_210213.pdf)

References

1. The Asahi Shimbun: *Health Ministry Withdraws Recommendation for Cervical Cancer Vaccine*. [June 2013]
2. National Institute of Neurological Disorders and Strokes: *Complex Regional Pain Syndrome Fact Sheet.* [Accessed: March 2014]
3. Cervarix® Package Insert. Malaysia. [Version: September 2012]
4. Gardasil® Package Insert. Malaysia. [Version: February 2011]
5. WHO Global Advisory Committee on Vaccine Safety (March 2014). *Statement on the continued safety of HPV vaccination.*
6. WHO Global Advisory Committee on Vaccine Safety (June 2013). *Weekly epidemiological record: Update on Human Papillomavirus Vaccines.* 29:309-312.

ALLOPURINOL: IMPACT OF RISK MINIMISATION ACTIONS

by Rema Panickar

Allopurinol was the top cause of severe adverse cutaneous drug reactions (ACDRs) reported in Malaysia between 2000 to 2012. This drug contributed to 17% (192 reports) of the total reports for Stevens-Johnson syndrome (SJS), 13% (28 reports) for toxic epidermal necrolysis (TEN), and 35% (53 reports) for drug reaction with eosinophilia and systemic symptoms (DRESS)[1].

This safety issue has been featured in previous editions of the MADRAC Bulletin (Dec 2008, Apr 2010, Dec 2010 and Aug 2012). Several risk minimisation measures have been implemented since 2004 to ensure rational use of this drug and reduce the incidence of ACDRs (***Table 2***). These measures have shown some promising results, with a 21% **decrease** in the total number of allopurinol **ADR reports** from 2011-2013, as well as a reduction in ADRs related to **use in unapproved indications.**

However, the number of **serious skin reactions remains high**, making up almost 40% (35 reports) of the total reports in 2013. The usage of allopurinol also displayed an increasing trend from 2012 to 2013 especially in Ministry of Health (MOH) facilities, with data showing a 20% increase. This fact raises concerns on whether the drug is being used according to the approved indications, as listed below. The NPCB continues to monitor this safety issue closely and will take further steps to ensure the safe and rational use of allopurinol.

Indications for allopurinol approved by the Drug Control Authority:

- Chronic gout/gouty arthritis
- Uric acid nephropathy
- Calcium oxalate renal calculi/ uric acid renal calculi
- Hyperuricemia secondary to:
  - cancer chemotherapy/ radiation therapy
  - blood dyscrasias
  - enzyme disorders

Advice for Healthcare Professionals:

- Allopurinol should be prescribed only for the approved indications as listed in the product package inserts or MOH drug formulary[2].
- Allopurinol should not be used to treat acute gout.
- Monitoring: Increased vigilance and dosage adjustments are required in patients with renal impairment, hepatic impairment, and those on diuretic therapy.
- Counselling: Patients must be informed to stop the drug and consult their doctor immediately if they develop any of the following signs or symptoms: fever, sore throat, fatigue, eye irritation, cough, rash, itching, swelling or joint pain
- Action: Allopurinol should be withdrawn immediately at the first sign of skin rash or other evidence of sensitivity.[3]

Table 2: Risk Minimisation Actions Related to Allopurinol

Year	Date	Risk Minimisation Action
2004	3 Aug	Advisory distributed to prescribers on approved indications of allopurinol – Ref: (30)dlm.BPFK/17/FV/2.3
2007	Jan	The Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) discusses allopurinol safety issue of increasing ADR reports, use in asymptomatic hyperuricaemia, and cases of serious skin reactions
2008	28 Nov	Circular from the Director General of Health regarding allopurinol ADRs and information for prescribers – KKM87/P1/19/1/0(12)
	Dec	Article in MADRAC Bulletin: *"SJS and TEN Associated With The Use of Allopurinol"*
2010	Apr	Article in MADRAC Bulletin: *"Allopurinol: Prescribing For The Right Indications"*
	Dec	Article in MADRAC Bulletin: *"Allopurinol-induced Adverse Cutaneous Drug Reactions"*
2011	2 Feb	Letter from NPCB to the Pharmacy Practice and Development Division on the suggestion by MADRAC to restrict usage and tighten the indication of allopurinol – Ref: (54)dlm.BPFK/17/FV/11
	19 Aug	Circular from the Director General of Health to remove uric acid analysis from routine renal profile results – KKM87/P1/19/1/0(25)
	25 Aug	Circular regarding the amendment of the FUKKM raising the allopurinol prescribing category from 'B' to 'A/KK' and tightening the indication of allopurinol- KKM-55/BPF/103/001/09Jld.13(55)
2012	12 Apr	MADRAC decision to issue reminder letters to prescribers who use allopurinol outside the approved indications, resulting in ADRs.
	Aug	Article in MADRAC Bulletin: *"Allopurinol: Update on Usage in MOH facilities and related Adverse Cutaneous Drug Reactions"*
2014	22 Apr	Letter from NPCB to all state health directors on ADR reporting for allopurinol, counselling and monitoring of patients – Ref: (60)dlm.BPFK/PASCA/FV/3 Jld 14

References:
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3. Zyloric® Package Insert, Malaysia. [Version: September 2011]

REGULATORY MATTERS

ORAL KETOCONAZOLE: RESTRICTION OF USE TO HOSPITALS AND TIGHTENING OF INDICATIONS

Ketoconazole is an imidazole fungicide available in both oral and topical formulations. The oral formulation has been associated with the risk of **potentially irreversible or life-threatening hepatotoxicity**, resulting in a directive being issued previously by the Drug Control Authority (DCA) in September 2011 to update the local package inserts with related warnings, contraindications and other safety information. The NPCB continued to monitor and review the risk-benefit profile of oral ketoconazole. Since 2001, the Drug Safety Monitoring Centre has received **26 ADR reports** with

47 adverse events related to oral ketoconazole. **Eight of the reports (30%)** were related to **hepatotoxicity**, with adverse events including jaundice (6), hepatitis (2), cholestatic hepatitis, and abnormal liver function test results. The remaining reports mainly involved skin disorders and allergic reactions such as rash, itching and photosensitivity. There were no reports with a fatal outcome.

Although hepatotoxicity is a known potential class effect of azole antifungals, the incidence and seriousness of hepatotoxicity is **higher with ketoconazole than with other antifungal agents.** This safety issue has also been reviewed by other international regulatory authorities. In the European Union, the European Medicines Agency (EMA) recommended suspension of the oral formulation due to negative risk-benefit assessments, while the United States Food and Drug Administration has limited the use to indications where the benefits outweigh the risks. Taking these facts into consideration, DCA agreed with the MADRAC recommendations and issued a directive in April 2014 [Ref: BPFK/PPP/07/25 (9)] restricting the use of oral ketoconazole to **hospitals only** and further **tightening the indications** as below:

Oral ketoconazole:

- Should be used only when **other effective antifungal therapy is not available** or tolerated and the potential benefits are considered to outweigh the potential risks.
- For the treatment of patients who have failed or are **intolerant** to other therapies of the following systemic fungal infections: blastomycosis, coccidiomycosis, histoplasmosis, chromomycosis, or paracoccidioidomycosis.
- **Should not** be used for fungal meningitis due to poor penetration into the cerebrospinal fluid.

SYNTHETIC CALCITONIN SALMON: RESTRICTION OF INDICATIONS AND DURATION OF USE

Calcitonin salmon is a hormone used in the regulation of calcium homeostasis to increase the amount of calcium in the bones and lower blood calcium levels. On 31 March 2014, the DCA on the advice of MADRAC issued a directive restricting the indications and duration of use for synthetic calcitonin salmon products (parenteral and nasal spray) [Ref: BPFK/PPP/07/25 (10)]. This was based on evidence of a small but statistically significant increased **risk of cancer** of various types (0.7-2.4%) with the long-term use of these medicines exceeding 6 months.

The Drug Safety Monitoring Centre, NPCB has received nine (9) suspected ADR reports with 19 events for calcitonin-containing medicines since 2000. Among the adverse events reported were nausea (3 events), muscle pain (2), vomiting (2), abdominal pain (1) and nasal discomfort (1).

Synthetic calcitonin salmon products should be used at the **minimum effective dose** for the **shortest possible time.** The restrictions of indication and duration of use are as listed below *(please refer to the current approved package inserts for full prescribing details):*

Dosage Form	New Restricted Indications	Maximum duration of treatment
Parenteral	Prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures	4 weeks
	For the treatment of Paget's disease, only in patients who do not respond to alternative treatments or for whom such treatments are not suitable	3 months
	Treatment of hypercalcaemia of malignancy	-
Nasal spray	Prevention of osteoporosis: In acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures.	3 months
	Paget's disease: Only in patients who do not respond to alternative treatments or for whom such treatments are not suitable	3 months
	Algodystrophy or Sudeck's Disease (neurodystrophic disorders) due to various causes and predisposing factors.	6 weeks

INTRAVENOUS ONDANSETRON: DOSE-DEPENDENT QT INTERVAL PROLONGATION

Ondansetron is a selective 5-hydroxytryptamine-3 (5-HT3)-receptor antagonist approved in Malaysia since 1995 for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, or for the prevention and treatment of post-operative nausea and vomiting.

Previously in September 2012, the product registration holder of the innovator product, Zofran®, issued a Direct Healthcare Professional Communication (DHPC) informing prescribers of the **reduction in maximum dose** of intravenous ondansetron due to the risk of clinically significant QT interval prolongation. Further analysis of these study results revealed that **elderly patients aged 75 years or older** required **additional precautionary measures**, as listed below. A second DHPC was issued on 14 April 2014 regarding dose-dependent QT interval prolongation which could lead to *Torsade de Pointes.*

Since the year 2001, the Drug Safety Monitoring Centre, NPCB has received 13 ADR reports with 17 adverse events related to ondansetron, all involving intravenous use. There were no reports concerning QT interval prolongation, high doses (dose range in reports: 4-8mg) or elderly patients (age range: 15-63 years). Most of the reports involved allergic effects such as injection site urticaria, rash, and periorbital oedema.

Summary of updated prescribing information for intravenous ondansetron:

- **Dosage and administration:**

  Elderly patients aged 75 years or older:
  - » *A single dose of intravenous ondansetron given for the prevention of chemotherapy-induced nausea and vomiting (CINV) must not exceed 8mg (infused over at least 15 minutes).*

  Adult patients aged less than 75 years:
  - » *A single dose of intravenous ondansetron given for the prevention of CINV in adults (aged less than 75 years) must not exceed 16mg (infused over at least 15 minutes).*

  Repeat dosing in all adult patients (including elderly patients):
  - » *Repeat intravenous doses of ondansetron for the prevention of CINV should be given no less than 4 hours apart.*

  Dilution and administration in elderly patients aged 65 years or older:
  - » *All intravenous doses of ondansetron for the prevention of CINV should be diluted in 50–100mL saline or other compatible fluid and infused over at least 15 minutes.*

- **Avoid** use in patients with congenital long QT syndrome.
- **Caution** in patients with risk factors for QT interval prolongation or cardiac arrhythmias.
- **Hypokalaemia and hypomagnesaemia** should be corrected prior to ondansetron use.

ERBITUX® (CETUXIMAB) AND VECTIBIX® (PANITUMUMAB): THE IMPORTANCE OF ESTABLISHING WILD-TYPE RAS STATUS (EXONS 2, 3, AND 4 OF KRAS AND NRAS) BEFORE TREATMENT IN METASTATIC COLORECTAL CANCER

Epidermal growth factor receptors (EGFRs) exist on the cell surface and are activated by binding of specific ligands, including epidermal growth factor and transforming growth factor alpha (TGFα). The identification of EGFR as an oncogene (a gene known to cause cancer) has led to the development of anticancer therapeutics directed against EGFR (called "EGFR inhibitors").

Erbitux® (cetuximab) and Vectibix® (panitumumab) are two EGFR inhibitors registered in Malaysia. Both products are indicated for the treatment of metastatic colorectal cancer (mCRC) *–please refer to the respective package inserts for full prescribing information.* Mutations of the genes known as KRAS and NRAS* have been associated with resistance to anti-EGFR therapy. Studies have shown mutations at exons 2, 3 and 4 in colorectal cancer. New efficacy and safety information from two studies (the PRIME study and the OPUS trial) have resulted in the recommendations listed below. Direct Healthcare Professional Communications (DHPCs) have been distributed for both products, and the package inserts will be updated with this new safety information.

Genetic testing for RAS status is currently arranged by the respective product registration holders, and is carried out either locally or outsourced. Test results are normally available within 5-20 working days.

Advice for Healthcare Professionals:

- Evidence of wildtype *RAS* status (at exons 2, 3 and 4 of *KRAS* and *NRAS*) is required before initiating treatment with cetuximab/ panitumumab.
- *RAS* mutation status should be determined by an experienced laboratory using a validated test method (contact product registration holder for details).
- Cetuximab/ panitumumab is contraindicated in combination with oxaliplatin-containing chemotherapy (e.g. FOLFOX) in all patients with mutant or unknown *RAS* status.

*Key:
KRAS: *Kirsten rat sarcoma viral oncogene homolog;* ***NRAS:*** *neuroblastoma RAS viral oncogene homolog;* ***PRIME study:*** *Panitumumab Randomised Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy;* ***OPUS trial:*** *Oxaliplatin and Cetuximab in First-Line Treatment of mCRC;* ***FOLFOX:*** *oxaliplatin plus continuous infusional 5-fluorouracil/folinic acid*

CYPROTERONE ACETATE 2MG AND ETHINYLESTRADIOL 0.035MG: MINIMISING THE RISK OF THROMBOEMBOLISM

The NPCB would like to inform all healthcare professionals that the local package inserts for combination products containing cyproterone acetate 2 mg and ethinylestradiol 0.035 mg (Diane 35® and its generics) are being updated. Following a benefit-risk assessment of these products by the Drug Safety Monitoring Centre, MADRAC agreed to **tighten the indications** and strengthen the warnings regarding the **risk of thromboembolism.** A safety update report has been distributed by the NPCB regarding this issue.

Combination products containing cyproterone acetate 2 mg and ethinylestradiol 0.035 mg (CPA/EE) have been registered in Malaysia since 1990 for the treatment of androgen dependent diseases in women. However, they are suspected to be widely used solely as contraceptives, outside the approved indications. Epidemiological studies have shown that CPA/EE carries a risk of venous thromboembolism (VTE) which is 1.5 to 2 times higher than combined-oral contraceptives (COCs) containing levonorgestrel, and may be similar to the risk of COCs containing desogestrel / gestodene / drosperinone.

Since 2000, the Drug Safety Monitoring Centre has received 12 ADR reports associated with CPA/EE, none involving VTE. The adverse events reported were nausea (3 events), vomiting (3), urticaria (2), constipation, diarrhoea, acne, photodermatitis, photosensitive rash, skin peeling, dizziness, headache, alpha-fetoprotein increased, hyperglycaemia, and appetite increased.

Advice for Healthcare Professionals:

- CPA/EE products are only indicated for the treatment of **moderate to severe acne** related to androgen-sensitivity (with/ without seborrhoea) and/or **hirsutism**, in women of reproductive age.
- For the treatment of acne, these medicines should **only be used after topical therapy or systemic antibiotic** treatment has **failed.**
- CPA/EE products **should not** be prescribed for the sole purpose of contraception. However, when taken as recommended, these products will provide reliable contraception in patients treated for the above clinical conditions.
- CPA/EE products are no longer indicated for the treatment of androgenetic alopecia.
- Patients must be **screened for risk factors of VTE** before beginning treatment with CPA/EE.
- The need to continue treatment with CPA/EE should be **reviewed periodically.**
- Patients should be **counselled** on the risk of thromboembolism with CPA/EE treatment, risk factors such as increasing age, smoking, obesity and prolonged immobility, and signs and symptoms to watch out for.

NEW ON THE BPFK PORTAL

SAFETY ALERTS FOR HEALTHCARE PROFESSIONALS

Brought to you by the Drug Safety Monitoring Centre, this section of the portal aims to update healthcare professionals on the latest drug safety issues handled by the NPCB. These alerts briefly highlight the issues affecting drugs registered in Malaysia, any regulatory actions taken, and new recommendations which may affect clinical practice. You will also be provided with details on where to obtain further information regarding each safety issue.

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