BERITA UBAT-UBATAN

Volume 66 | No.46 | ISSN 0128-0627

EVENTS

FINALIZATION OF ASEAN TRADITIONAL MEDICINES AND HEALTH SUPPLEMENTS (TMHS) GMP TRAINING MODULES PHASE 1C

On the third quarter of 2016, a meeting for the finalization of ASEAN Traditional Medicines and Health Supplements (TMHS) GMP Training Modules Phase 1C was held on 22-25th August 2016 at the Royale Chulan Damansara, Petaling Jaya where 9 out of 11 training modules have been successfully updated following results from the discussions achieved among 27 representatives of ASEAN countries.

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DCA EDITORIAL TEAM

The meeting was attended by participants from 10 ASEAN countries consisting of 24 official representatives and 3 representatives from the industries. The National Pharmaceutical Regulatory Agency (NPRA), as an official representative body by the Ministry of Health were the host sent a total of 5 participants including the chairman of the ASEAN Task Force TMHS GMP.

The development of ASEAN GMP TMHS training modules is one of the activities under the development plan of the ASEAN guidelines for Good Manufacturing Practice (GMP) for Traditional Medicines and ASEAN Good Manufacturing Practice (GMP) for Health Supplements. Both of these guidelines are joint ASEAN TMHS GMP Task Force led by Malaysia under the ASEAN Consultative Committee on Standards and Quality (ACCSQ) TMHS Product Working Group (PWG) for the purpose of harmonization in regulatory requirements of GMP for products of traditional and health supplements in the ASEAN region. This initiative aims to avoid the technical barriers resulting from variances in regulatory requirements set among ASEAN country members without compromising the safety, quality and efficacy of a product.

Among the benefits to be gained through the organization of this meeting in Malaysia are:

- to allow more representatives from the NPRA to attend the meeting;
- to provide an opportunity for the participants to share their views with each other and thus building a network of working relationships between the two countries involved;
- to promote the development of regulatory aspects of GMP for TMHS products in Malaysia.

This meeting were beneficial to regulators and traditional products and health supplements industries of the ASEAN region by giving way to the harmonization of regulatory requirements of GMP. This meeting is a continuous effort in forging stronger regional cooperation. Throughout the meetings among

representatives of the ASEAN countries, regulatory issues related to the TMHS products has been discussed.

NEW DIRECTIVES

The following directives have been issued under the Regulation 29 of the Control of Drugs and Cosmetics Regulations 1984 by the Senior Director of Pharmaceutical Services, YBhg. Dr Salmah Bahri.

1. ***Directive No. 15 Year 2016 [Ref: (1) dlm. BPFK/PPP/07/25 Jld 1]: Safety updates in product package insert pertaining to the risk of calciphylaxis for all products containing warfarin***

Following the decision made by the Drug Control Authority (DCA) in its 304th Meeting on 27th September 2016, this directive was issued to enforce the said safety updates. The following safety updates shall be included in package insert of all products containing warfarin:

Special Warnings and Precautions for Use: *(In package insert)*

Calciphylaxis

Calciphylaxis is a rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis or in patients with known risk factors such as protein C or S deficiency, hyperphosphatemia, hypercalcaemia or hyperalbuminaemia. Rare cases of calciphylaxis have been reported in patients taking warfarin, also in the absence of renal disease. In case calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin.

Adverse Drug Reactions: *(In package insert)*

Skin and subcutaneous tissue disorders

Frequency 'not known': Calciphylaxis

Possible Side Effects: *(In RiMUP)*

Tell your doctor straight away if you have any of the following side effects:

A pain skin rash. On rare occasion warfarin can cause serious skin conditions, including one called calciphylaxis that can start with a painful skin rash but can lead to other serious complications. This adverse reaction occurs more frequently in patients with chronic kidney disease.

Effective date of this safety updates package insert is as follows:

New registration and products under evaluation: **1st November 2016**
Registered products: **1st May 2017**

The said safety updates for the registered products shall be done via variation application. This directive came into force starting from **1st November 2016.**

2. ***Directive No. 16 Year 2016 [Ref: (2) dlm. BPFK/PPP/07/25 Jld 1]: Safety updates in product package insert pertaining to the risk of respiratory depression for all products containing codeine***

Following the decision made by the Drug Control Authority (DCA) in its 304th Meeting on 27th September 2016, this directive was issued to enforce the said safety updates. The following safety updates shall be included in package insert of all products containing codeine:

Therapeutic Indications: *(In package insert)*

[Product name] is indicated for the relief of painful disorders such as headache, dysmenorrhea, and conditions involving musculoskeletal pain, myalgias and neuralgias. It is also indicated as an analgesic and antipyretic in conditions accompanied by discomfort and fever, such as the common cold and viral infections. [Product name] is an effective analgesic after dental work and tooth extractions.

Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

Dosing and Administrations: *(In package insert)*

Paediatric population:

- *Children aged less than 12 years:*
  Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine.

  [Product name] is contraindicated in children below the age of 12 years for the symptomatic treatment of cold.

- *Children aged 12 years to 18 years*
  [Product name] is not recommended for use in children aged 12 years to 18 years with compromised respiratory function.

Contraindications: *(In package insert)*

- *In children below the age of 12 years for the symptomatic treatment of colds due to an increased risk of developing serious and life threatening adverse reactions.*
- *In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to increased risk of developing serious and life threatening adverse reactions.*
- *In women who are breastfeeding*
- *In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers*

Special Warnings and Precautions for use: *(In package insert)*

CYP2D6 metabolism

- *Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.*

  General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal.

Special Warnings and Precautions for use: *(In package insert)*

CYP2D6 metabolism

- *Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized below:*

Population	*Prevalence %*
African/Ethiopian	*29%*
African American	*3.4 to 6.5%*
Asian	*1.2 to 2.0%*
Caucasian	*3.6 to 6.5%*
Greek	*6.0%*
Hungarian	*1.9%*
Northern European	*1.0 to 2.0%*

Post –operative use in children

- *There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life threatening adverse events including death. All children receiving doses of codeine that were within the appropriate dose range; there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.*

Children with compromised respiratory function

- *Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory of lung infections, multiple trauma or extensive surgical procedures. These factor may worsen symptoms of morphine toxicity.*

Pregnancy and Lactation: *(In package insert)*

Pregnancy

- *Careful consideration should be given before prescribing the product for pregnant patients. Opioid analgesics may depress neonatal respiration and cause withdrawal effects in neonates of dependent mothers.*

  As a precautionary measure, use of [Product name] should be avoided during the third trimester of pregnancy and during labor.

Breastfeeding

- *[Product name] is contraindicated in women during breastfeeding. At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine may be present in breast milk and on very rare occasion may result in symptoms of opioid toxicity in the infant, which may be fatal.*

Effective date of this safety updates package insert is as follows:

New registration and products under evaluation: **1st November 2016**
Registered products: **1st May 2017**

The said safety updates for the registered products shall be done via variation application. This directive came into force starting from **1st November 2016.**

3. ***Directive No. 17 Year 2016 [Ref: (3) dlm. BPFK/PPP/07/25 Jld 1]: Safety updates in product package insert pertaining to the risk abnormal pregnancy outcomes for all products containing sodium valproate***

Following the decision made by the Drug Control Authority (DCA) in its 304th Meeting on 27th September 2016, this directive was issued to enforce the said safety updates. The following safety updates shall be included in package insert of all products containing sodium valproate:

Posology and Method of Administration: *(In package insert)*

Female children, female adolescents, women of childbearing potential and pregnant women

- *[Product name] should be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably [Product Name] should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses.*

Special Warnings and Precaution for use: *(In package insert)*

Female children, female adolescents, women of childbearing potential and pregnant women

- *[Product name] should not be used in female children, female adolescents, women of childbearing potential and pregnant women unless alternative treatment are ineffective or not tolerated because of high teratogenic potential and risk of developmental disorders in infant exposed in utero to valproate.*
- *The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with [Product Name] plans a pregnancy or if she becomes pregnant.*

- *Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of [Product Name] during pregnancy.*
- *The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks.*
- *In particular the prescriber must ensure the patient understands:*
    - *The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.*
    - *The need to use effective contraception.*
    - *The need for regular review of treatment.*
    - *The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.*
- *In women planning to become pregnant all efforts should be made to switch appropriate alternative treatment prior to conception, if possible.*
- *Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by physician experienced in the management of epilepsy.*

Fertility, pregnancy and lactation: *(In package insert)*

[Product name] should not be used in female children, female adolescents, women of childbearing potential and pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate treatment prior to conception, if possible

<u>Pregnancy Exposure Risk related to valproate</u>

- *Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.*

<u>Congenital malformations</u>

- *Data derived from meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established. Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), multiple anomalies involving various body systems.*

Developmental disorders

- *Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.*
- *Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.*
- *Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ. There are limited data on the long term outcomes.*
- *Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared to the general study population.*
- *Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).*

Female children, female adolescents, women of childbearing potential and pregnant women

If a woman wants to plan a pregnancy:

- *During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child.*
- *In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed.*
- *In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to concepton, if possible.*

Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment. If based on careful evaluation of the risks and the benefits valproate treatment is continued during pregnancy, it is recommended to:

- *Use the lowest effective dose and divide daily dose valproate into several small doses to be taken throughout the day.*
- *The use of prolonged release formulation in order to avoid high peak plasma concentrations.*
- *Folate supplementation before pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.*
- *To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.*

Effective date of this safety updates package insert is as follows:

New registration and products under evaluation: **1st November 2016**
Registered products: **1st May 2017**

The said safety updates for the registered products shall be done via variation application. This directive came into force starting from **1st November 2016.**

SUMMARY OF PRESS RELEASE

TRADITIONAL PRODUCTS / HEALTH SUPPLEMENTS

A) *Caution on Using Unregistered Traditional Products Containing Scheduled Poisons*

The National Centre for Adverse Drug Reactions Monitoring, NPRA would like to remind the public not to buy or use the following unregistered products:

Product Name	Registration Number	Adulterant Detected	Description
Super Resdong	MAL06051618T) (Fake)	Dexamethasone Chlorpheniramine	Brownish Pill
Mujarab Resdong Plus	MAL06051618T) (Fake)	Dexamethasone Chlorpheniramine	Brownish Pill

The traditional product labelled as *"Super Redong"* and *"Mujarab Resdong Plus*" were proven to contain adulterants of dexamethasone and chlorpheniramine after sampling of the product were made through adverse reaction reports received by the National Centre for Adverse Drug Reactions Monitoring (NPRA).

The labels on both products states that these products are traditionally used to relieve "*resdong"* and signs of nasal irritation. Review confirms that the two products are not registered with the DCA and is a product that needs to be registered. Registration number printed on the labels of both products is the same (MAL06051618T) and found to be false.

The NPRA received a total of four (3) reports of adverse events product involving *"Super Redong"* and eight (1) reports of adverse events involving *"Mujarab Resdong Plus*" product. Among the adverse events reported is inflammation of the liver (hepatitis), kidney problems, weight gain and rashes on the body.

Dexamethasone and chlorpheniramine are controlled under the Poisons Act 1952. Dexamethasone is a potent corticosteroid and used for the treatment of swelling and serious inflammation problems. Long term unsupervised use of dexamethasone can lead to serious side effects that can be harmful to health such as muscle weakness, bone loss, increased in blood sugar levels leading to diabetes, high blood pressure, glaucoma and an increased risk of infections.

Consumer can also experience Cushing's syndrome which is characterized by a rounded face and enlarged upper part of body but shrinkage of arms and legs. Patients with chronic diseases such as diabetes, poses higher risk and are advised not to use unregistered items as they may be adulterated with corticosteroids. Corticosteroids can cause uncontrolled blood sugar levels and therefore cause serious complications. Whereas, Chlorpheniramine is used to relieve colds and allergic reactions such as rashes. Chlorpheniramine side effects include drowsiness, blurred vision, vomiting, constipation and weakness of limbs coordination.

Any scheduled poison is not allowed to be formulated in a product which is classified as a traditional product under the Sale of Drug Act 1952 and Control of Drugs and Cosmetics Regulations 1984. All sellers are warned to stop sales and distribution of this product. Individuals who commit an offence under these laws will face penalty up to RM25, 000 and or imprisonment for a period of (3) years for the first offence, and penalty up to RM50, 000 and or imprisonment for a period up to five (5) years for a subsequent offence. A company found guilty can be fined up to RM50, 000 for the first offence and a fine of up to RM100, 000 for a subsequent offence.

The public is advised not to buy or consume products that are not registered with the DCA or with fake registration number as their quality and safety are not known.

CONTACTS & MAP

National Pharmaceutical Control Bureau (NPCB)	+ 603 - 7883 5400

CENTRES	EXTENSION NO.
Centre for Product Registration – Deputy Director	ONE-STOP CALL CENTRE 5511
• Active Pharmaceutical Ingredient Section	
• Biotechnology Section	
• Complementary Medicine Section	
• Generic Medicine Section	
• New Drug Section	
• Regulatory Coordination Section	
• Veterinary Medicine Section	
Centre for Post-Registration of Products – Deputy Director	5538
• Cosmetic Section	5532
• Pharmacovigilance Section	5543
• Surveillance and Product Complaints Section	5552
Centre for Investigational New Product – Deputy Director	5581
• BE Centre & Ethics Committee Compliance Section	8403
• GCP Compliance Section	8401
• GLP Compliance Section	8404
• Investigational Product Evaluation Section	8406
• Investigational Product Safety Monitoring Section	8405
Centre for Compliance and Licensing – Deputy Director	5564
• GDP Section	5568
• GMP 1 Section	5566
• GMP 2 Section	5567
• Licensing and Certification Section	5569
• Quality and Industry Development Section	8556
Centre for Organisational Development – Deputy Director	5553
• Helpdesk	5560, 5561, 5562
• Information and Communications Technology Section	5555
• Quality, Competency & Communication Coordination Section	8481
Centre for Quality Control – Deputy Director	5429
• Bio-Pharmaceutical Testing Section	8894
• Complementary Medicines Testing Section	8892
• Laboratory Services Section	5431
• Pharmaceutical Chemistry Testing Section	8490
• Reference Standard Section	5468
• Research Section	8446
Centre for Administration	8458

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