BIRO PENGAWALAN FARMASEUTIKAL KEBANGSAAN
NATIONAL PHARMACEUTICAL CONTROL BUREAU
Kementerian Kesihatan Malaysia
Ministry of Health Malaysia
Lot 36 Jalan Universiti
46200 Petaling Jaya
Selangor Darul Ehsan
MALAYSIA

Tel. : +603-7883 5400
Faks (*Fax*) : +603-7956 2924
Laman Web (*Web*) : www.bpfk.gov.my

Ruj. Kami: (2) dlm. BPFK/PPP/07/25 Jld. 1
Tarikh : 11/10/16

SEMUA PEMEGANG PENDAFTARAN

SEMUA PERSATUAN BERKENAAN
(SEPERTI DI SENARAI EDARAN)

Tuan/ Puan,

PERATURAN-PERATURAN KAWALAN DADAH DAN KOSMETIK 1984
ARAHAN PENGARAH KANAN PERKHIDMATAN FARMASI BILANGAN 16 TAHUN 2016: DIREKTIF BAGI SEMUA PRODUK YANG MENGANDUNGI CODEINE DENGAN MAKLUMAT KESELAMATAN BERKAITAN RISIKO KESAN ADVERS *RESPIRATORY DEPRESSION*

Adalah saya merujuk kepada Arahan Bilangan 16 Tahun 2016 oleh Pengarah Kanan Perkhidmatan Farmasi.

2. Dimaklumkan bahawa Pengarah Kanan Perkhidmatan Farmasi, Kementerian Kesihatan Malaysia dalam Arahan Bilangan 16 Tahun 2016 telah bersetuju untuk menambah maklumat keselamatan berkaitan risiko kesan advers *respiratory depression* bagi semua produk yang mengandungi codeine seperti pada surat arahan Bil. (2) BPFK/PPP/07/25 Jld. 1.

3. Pihak pemegang pendaftaran adalah diarahkan untuk mematuhi keperluan tersebut.

Sekian, terima kasih.

"BERKHIDMAT UNTUK NEGARA"

Saya yang menurut perintah,

(DR. SALMAH BT. BAHRI)
Pengarah Regulatori Farmasi
Agensi Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia
ra/nb/ppp/NPRA/071016

BPFK/PPP/07/25 (2) Jld 1

ARAHAN DI BAWAH PERATURAN 29 PERATURAN – PERATURAN KAWALAN DADAH DAN KOSMETIK 1984

BILANGAN 16 TAHUN 2016

DIREKTIF BAGI SEMUA PRODUK YANG MENGANDUNGI CODEINE DENGAN MAKLUMAT KESELAMATAN BERKAITAN RISIKO KESAN ADVERS *RESPIRATORY DEPRESSION*

TUJUAN

1.1 Arahan ini dikeluarkan oleh Pengarah Kanan Perkhidmatan Farmasi di bawah Peraturan 29 (1) Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984.

1.2 Arahan ini ditujukan kepada semua produk yang mengandungi codeine dengan menambah maklumat keselamatan berkaitan risiko kesan advers *respiratory depression.*

LATAR BELAKANG

2.1 Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke **304** pada **27 September 2016** telah membuat keputusan bagi semua produk yang mengandungi codeine untuk menambah maklumat keselamatan berkaitan risiko kesan advers *respiratory depression.*

PELAKSANAAN

3.1 Oleh itu, maklumat keselamatan berkaitan risiko kesan advers *respiratory depression* perlu ditambah pada sisip bungkusan bagi semua produk yang mengandungi codeine dengan memperketatkan dan menyelaraskan maklumat pada bahagian *Therapeutic Indications, Dosing and Administrations, Contraindications, Special Warnings and Precautions for Use,* dan *Pregnancy and Lactation* seperti berikut:-

3.1.1 Pada bahagian ***Therapeutic Indications***

[Product name] is indicated for the relief of painful disorders such as headache, dysmenorrhea, 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).

3.1.2 Pada bahagian ***Dosing and Administrations***

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.

3.1.3 Pada bahagian ***Contraindications***

- *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.*

3.1.4 Pada bahagian ***Special Warnings and Precautions for use***

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. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised 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 received doses of codeine that were within the appropriate dose range; however 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 or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

3.1.5 Pada bahagian ***Pregnancy and Lactation***

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 occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

4. Tarikh pelaksanaan keperluan mengemaskini maklumat berkenaan pada semua produk yang mengandungi codeine bagi:

(a) Permohonan baru dan produk yang sedang dalam proses penilaian : **1 November 2016**

(b) Produk berdaftar : **1 Mei 2017**

5. Permohonan pindaan pada sisip bungkusan bagi produk berdaftar perlu dikemukakan sebagai permohonan variasi.

6. Tarikh kuat kuasa arahan ini ialah mulai **1 November 2016.**

"BERKHIDMAT UNTUK NEGARA"

(DR. SALMAH BT. BAHRI)
Pengarah Regulatori Farmasi
b.p Pengarah Kanan Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia

rainb/ppp/NPRA/061016

s.k. 1. Pengarah Regulatori Farmasi
Agensi Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia.

2. Pengarah Penguatkuasa Farmasi
Bahagian Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia.

3. Pengarah Amalan dan Perkembangan Farmasi
Bahagian Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia.