



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: (32) dlm. BPFK/PPP/07/25 Jld. 1

Tarikh : 12 DEC 2017

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 27 TAHUN 2017: DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI OPIOID: PENGEMASKINIAN SISIP BUNGKUSAN DAN RISALAH MAKLUMAT UBAT UNTUK PENGGUNA (RiMUP) DENGAN MAKLUMAT KESELAMATAN BERKAITAN RISIKO KESAN ADVERS *SEROTONIN SYNDROME* KESAN DARIPADA INTERAKSI DENGAN *SEROTONERGIC DRUGS* DAN RISIKO KESAN ADVERS *ADRENAL INSUFFICIENCY* DAN *ANDROGEN DEFICIENCY* AKIBAT PENGGUNAAN JANGKA PANJANG

Adalah saya merujuk kepada Arahan Bilangan 27 Tahun 2017 oleh Pengarah Kanan Perkhidmatan Farmasi.

2. Dimaklumkan bahawa Pengarah Kanan Perkhidmatan Farmasi, Kementerian Kesihatan Malaysia dalam Arahan Bilangan 27 Tahun 2017 telah bersetuju untuk menambah maklumat keselamatan berkaitan risiko kesan advers *serotonin syndrome* kesan daripada interaksi dengan *serotonergic drugs* dan risiko kesan advers *adrenal insufficiency* dan *androgen deficiency* akibat penggunaan jangka panjang bagi semua produk yang mengandungi opioid seperti pada surat arahan Bil.(32)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 RAMLI ZAINAL (RPh 1045)

Pengarah Regulatori Farmasi
Bahagian Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia

ra/nb/PPP/NPRA/281117

✉ rosilawati.a@npra.gov.my/ nurhidayah@npra.gov.my
☎ +603 - 7801 8423 / 8417
☎ +603 - 7958 1312

SITI AIDA BINTI ABDULLAH (RPh 1028)
Timbalan Pengarah (JUSA C)
Pusat Pembangunan & Perancangan Strategik
Bahagian Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia



Certified to ISO 9001 : 2008
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Member of
Pharmaceutical Inspection
Cooperation Scheme



Non Member Adherence to
Mutual Acceptance
of Data for GLP



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

BILANGAN 27 TAHUN 2017

**DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI OPIOID:
PENGEMASKINIAN SISIP BUNGKUSAN DAN RISALAH MAKLUMAT
UBAT UNTUK PENGGUNA (RiMUP) DENGAN MAKLUMAT
KESELAMATAN BERKAITAN RISIKO KESAN ADVERS *SEROTONIN
SYNDROME* KESAN DARIPADA INTERAKSI DENGAN *SEROTONERGIC
DRUGS* DAN RISIKO KESAN ADVERS *ADRENAL INSUFFICIENCY* DAN
ANDROGEN DEFICIENCY AKIBAT PENGGUNAAN JANGKA PANJANG**

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 pemegang pendaftaran produk yang mengandungi opioid bagi mengemaskini sisip bungkus dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko kesan advers *serotonin syndrome* kesan daripada interaksi dengan *serotonergic drugs* dan risiko kesan advers *adrenal insufficiency* dan *androgen deficiency* akibat penggunaan jangka panjang.

LATAR BELAKANG

2.1 Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke **318** pada **27 November 2017** telah membuat keputusan bagi semua produk yang mengandungi opioid untuk mengemaskini sisip bungkus dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko kesan advers *serotonin syndrome* kesan daripada interaksi dengan *serotonergic drugs* dan risiko kesan advers *adrenal insufficiency* dan *androgen deficiency* akibat penggunaan jangka panjang.

PELAKSANAAN

3.1 Oleh itu arahan – arahan berikut perlu dipatuhi untuk semua produk yang mengandungi opioid seperti berikut:-

3.1.1 Sisip bungkusan

Pada bahagian *Warnings and Precautions*:

Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of <product name> with serotonergic drugs (See Interactions with Other Medicaments). This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (See Interactions with Other Medicaments). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue <product name> if serotonin syndrome is suspected.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Sexual Function/Reproduction

Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (See Postmarketing Experience)

Pada bahagian *Adverse Effects/Undesirable Effects*:

Postmarketing Experience:

Serotonin syndrome (See Warnings and Precautions)

Adrenal insufficiency (See Warnings and Precautions)

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

Pada bahagian *Interactions with Other Medicaments:*

Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue <product name> if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT₃ receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (See Warnings and Precautions).

3.1.2 Risalah Maklumat Ubat Untuk Pengguna (RiMUP)

Pada bahagian *While you are using it <product name>:*

Things to be careful of:

- *Serotonin syndrome: <Product name> may cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. If you have some or all of these symptoms: feeling confused, feeling restless, sweating, shaking, shivering, hallucinations, sudden jerks in your muscles or a fast heartbeat, seek medical attention immediately.*
- *Adrenal insufficiency: Long-term use of <product name> may cause adrenal insufficiency, a potentially life-threatening condition that may present with non-specific symptoms and signs such as nausea,*

vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. Seek medical attention if you experience a constellation of these symptoms.

- *Infertility: Long-term use of <product name> may cause reduced fertility. It is not known whether these effects on fertility are reversible.*

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

(a) Permohonan baru dan produk yang sedang dalam proses penilaian : **1 Januari 2018**

(b) Produk berdaftar : **1 Jun 2018**

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

6. Tarikh kuat kuasa arahan ini ialah mulai **1 Januari 2018.**

“BERKHIDMAT UNTUK NEGARA”



(DR. SALMAH BT BAHRI) RPh. 783
Pengarah Kanan Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia

ra/nb/PPP/PRA/281117

- s.k.
1. Pengarah Regulatori Farmasi
Bahagian Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia
 2. Pengarah Amalan dan Perkembangan Farmasi
Bahagian Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia
 3. Pengarah Penguatkuasa Farmasi
Bahagian Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia