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Tarikh : 17 OCT 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 23 TAHUN 2017: DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI OPIOID DAN BENZODIAZEPIN: PENGEMASKINIAN SISIP BUNGKUSAN DAN RISALAH MAKLUMAT UBAT UNTUK PENGGUNA (RiMUP) DENGAN MAKLUMAT KESELAMATAN BERKAITAN INTERAKSI UBAT

Adalah saya merujuk kepada Arahan Bilangan 23 Tahun 2017 oleh Pengarah Kanan Perkhidmatan Farmasi.

2. Dimaklumkan bahawa Pengarah Kanan Perkhidmatan Farmasi, Kementerian Kesihatan Malaysia dalam Arahan Bilangan 23 Tahun 2017 telah bersetuju untuk menambah maklumat keselamatan berkaitan interaksi ubat bagi semua produk yang mengandungi opioid dan benzodiazepin seperti pada surat arahan Bil. (28) 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

SITI AIDA ABDULLAH
Timbalan Pengarah
Pusat Pembangunan Organisasi
Biro Pengawalan Farmaseutikal Kebangsaan
Kementerian Kesihatan Malaysia

ra/nb/ppp/NPRA/091017

BPFK/PPP/07/25 (28) Jld 1

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

BILANGAN 23 TAHUN 2017

DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI OPIOID DAN BENZODIAZEPIN: PENGEMASKINIAN SISIP BUNGKUSAN DAN RISALAH MAKLUMAT UBAT UNTUK PENGGUNA (RiMUP) DENGAN MAKLUMAT KESELAMATAN BERKAITAN INTERAKSI UBAT

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 semua produk yang mengandungi opioid dan benzodiazepin bagi mengemaskini sisip bungkusan dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat keselamatan berkaitan interaksi ubat.

LATAR BELAKANG

2.1 Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke **316** pada **3 Oktober 2017** telah membuat keputusan bagi semua produk yang mengandungi opioid dan benzodiazepin untuk mengemaskini sisip bungkusan dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat keselamatan berkaitan interaksi ubat.

PELAKSANAAN

3.1 Oleh itu arahan – arahan berikut perlu dipatuhi untuk semua produk yang mengandungi opioid seperti **alfentanil, buprenorphine, codeine, dihydrocodeine, fentanyl, methadone, morphine, nalbuphine, oxycodone, pentazocine, pethidine, remifentanil, tapentadol dan tramadol**, dan produk yang mengandungi benzodiazepin seperti **alprazolam, bromazepam,**

chlordiazepoxide, clobazam, clonazepam, clorazepate potassium, diazepam, lorazepam, midazolam, nitrazepam dan triazolam seperti berikut:-

3.1.1 Sisip bungkusan untuk produk yang mengandungi opioid

Pada bahagian *Warnings and Precautions:*

Risks from Concomitant Use with Benzodiazepines

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of <product name> with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.

If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when <product name> is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (See Drug Interactions).

Pada bahagian *Drug Interactions:*

Benzodiazepines
Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.

The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the

central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions).

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

3.1.2 Risalah Maklumat Ubat Untuk Pengguna (RiMUP) untuk produk yang mengandungi opioid

Pada bahagian *Taking other medicines:*

Taking <product name> with a benzodiazepine (medicine used as sedatives or to treat anxiety) can depress your central nervous system. Inform your doctor if you are currently taking any benzodiazepine.

Seek medical attention immediately if you or the person taking this medication experience(s) symptoms of unusual dizziness or lightheadedness, extreme sleepiness, slowed or difficult breathing, or unresponsiveness.

3.1.3 Sisip bungkusan untuk produk yang mengandungi benzodiazepin

Pada bahagian *Warnings and Precautions:*

<u>Risks from Concomitant Use with Opioids</u>

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of <product name> with opioids. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine

than indicated in the absence of an opioid, and titrate based on clinical response.

If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when <product name> is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of opioids (See Drug Interactions).

Pada bahagian *Drug Interactions:*

Opioids
Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.

The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions).

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

3.1.4 Risalah Maklumat Ubat Untuk Pengguna (RiMUP) untuk produk yang mengandungi benzodiazepin

Pada bahagian *Taking other medicines:*

Taking <product name> with an opioid medicine (medicine to relieve pain) can depress your central nervous system. Inform your doctor if you are currently taking any opioid medicine.

Seek medical attention immediately if you or the person taking this medication experience(s) symptoms of unusual dizziness or lightheadedness, extreme sleepiness, slowed or difficult breathing, or unresponsiveness.

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

(a) Permohonan baru dan produk yang sedang dalam proses penilaian : **1 November 2017**

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

"BERKHIDMAT UNTUK NEGARA"

MOHD YUNOS BIN SHAARI, RPh 1079
Pengarah
Lembaga Farmasi Malaysia
Kementerian Kesihatan Malaysia

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

ra/nb/ppp/NPRA/061017

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