BERITA UBAT-UBATAN

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KANDUNGAN

PROGRAM LATIHAN SISTEM REGULATORI FARMASEUTIKAL

Bahagian Regulatori Farmasi Negara (NPRA), KKM telah menganjurkan *Program Latihan Sistem Regulatori Farmaseutikal* ini dengan jayanya pada 25 - 29 September 2017 di NPRA, Petaling Jaya.

Seramai dua belas orang peserta dari sepuluh buah negara telah menyertai latihan ini. Program latihan ini juga adalah salah satu daripada aktiviti yang tersenarai dalam pelan implementasi OIC *Strategic Health Plan of Action* 2014 - 2023 di bawah *Thematic Area 4: Medicines, Vaccines and Medical Technologies.*

Objektif *Training Programme: Pharmaceutical Regulatory System 2017* ini adalah untuk:

(i) memberi pendedahan kepada anggota agensi regulatori/ pihak kerajaan negara tertentu berkaitan sistem regulatori di Malaysia yang maju dan sejajar dengan keperluan regulatori farmaseutikal di peringkat antarabangsa; dan

(i) menunjukkan komitmen Kementerian Kesihatan Malaysia terhadap tanggungjawabnya dalam memastikan produk terapeutik yang dipasarkan adalah berkualiti, selamat dan berkesan.

Di antara maklumbalas yang diterima selepas program latihan ini, pihak MOPI telah memaklumkan bahawa anggota agensi regulatori ubat dari negara-negara yang telah menjalankan latihan sangkutan di NPRA adalah lebih reseptif terhadap produk farmaseutikal buatan Malaysia dan mereka mendapati proses untuk mendaftar serta memasarkan produk mereka adalah lebih mudah jika dibandingkan dengan negara-negara yang tidak mengenali sistem regulatori di Malaysia.

DIREKTIF – DIREKTIF BARU

Arahan-arahan ini dikeluarkan oleh Pengarah Kanan Perkhidmatan Farmasi di bawah peraturan 29 (1), Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984, YBrs. Dr. Salmah Bahri.

1. DIREKTIF 21/17 [RUJ: (26) DLM. BPFK/PPP/07/25 JLD. 1]: PENGGUNAAN LABEL KESELAMATAN HOLOGRAM MEDITAG™ 4

Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke-316 pada 3 Oktober 2017 telah membuat keputusan bagi pelaksanaan penggunaan label keselamatan hologram meditag^{tm} 4 seperti berikut:

Ciri-ciri dan Maklumat Tambahan Label Keselamatan Hologram Meditag^{tm} 4

1. Meditag^{tm} 4 menggunapakai kaedah Data Matriks dan proses identifikasi label yang hanya menggunakan telefon pintar oleh pengguna, diharapkan dapat membantu mengukuhkan kawalan dan keselamatan produk farmaseutikal serta memperkasakan pengguna untuk memilih ubat yang berdaftar di pasaran. Keupayaan Meditrace yang selari dengan GS1 ini juga dijangkakan memberi kelebihan pada pihak industri jika mereka ingin menggunakannya.

2. Meditag^{tm} 4 mempunyai aplikasi pengesanan pendaftaran produk dimana keterangan berkenaan produk itu akan dipamerkan setelah diimbas menggunakan telefon pintar.

3. Nombor siri label keselamatan hologram Meditag^{tm} 4 dilengkapi nombor siri baru bagi bentuk 'Roll' iaitu bermula dengan G00000001 (G + 8digit) manakala bagi bentuk 'Sheet' adalah 00000001A (8digit + A).

4. Saiz label Meditag^{tm} 4 adalah saiz terdahulu iaitu 8mm x 16mm.

5. Tiada implikasi tambahan kos kepada pihak industri dan kerajaan berikutan ciri-ciri dan penambahbaikan dari Meditag^{tm} 3 kepada Meditag^{tm} 4 .

6. Pihak Mediharta akan bekerjasama dengan pihak Penguatkuasaan Farmasi dalam usaha untuk memberi latihan mengenai ciri-ciri baharu label keselamatan Meditag^{tm} 4 beserta pelaksanaan kempen kesedaran ke seluruh negara.

Tarikh pelaksanaan penggunaan label keselamatan hologram meditag^{tm} 4 mulai dari **12 Oktober 2017**. Walaubagaimanapun, stok label keselamatan hologram sedia ada yang masih di dalam simpanan pihak pengilang/pengimport masih boleh digunakan sehingga habis.

2. DIREKTIF 22/17 [RUJ: (27) DLM. BPFK/PPP/07/25 JLD. 1]: KEMASKINI SISIP BUNGKUSAN DAN RiMUP DENGAN MAKLUMAT KESELAMATAN BERKAITAN RISIKO KESAN ADVERS *PATHOLOGICAL GAMBLING* DAN *IMPULSE-CONTROL PROBLEMS* UNTUK SEMUA PRODUK FARMASEUTIKAL YANG MENGANDUNGI ARIPIPRAZOLE

Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke-316 pada 3 Oktober 2017 telah membuat keputusan bagi semua produk farmaseutikal yang mengandungi aripiprazole untuk mengemaskini sisip bungkusan dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat keselamatan mengenai risiko kesan advers seperti berikut:

Warnings and Precautions (sisip bungkusan)

Pathological gambling and impulse-control problems

Patients can experience increased urges, particularly for gambling and the inability to control these urges while taking aripiprazole. Other urges reported include: increased sexual urges, compulsive shopping, binge or compulsive eating, and other impulsive and compulsive behaviours.

It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however in some cases urges were reported to have stopped when the dose was reduce or the medication was discontinued. Patients who are at higher risk for impulse-control problems (e.g. personal or family history of obsessive-compulsive disorder, impulse-control disorder, bipolar disorder, impulsive personality, alcoholism, drug abuse or other addictive behaviours) would require closer monitoring for new or worsening of uncontrollable urges. Impulse-control problems may result in harm to the patient and others if not recognised. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole.

Undesirable Effects/Side Effects (sisip bungkusan)

Psychiatric disorders

Pathological gambling, hypersexuality, impulse-control problems (See Section Warning and Precautions).

Before you use <product name> (RiMUP)

Tell your doctor or pharmacist if you have:

- *A history of excessive gambling or other unusual urges (e.g. increased sexual urges, binge or compulsive eating and compulsive shopping).*

*Effects/Side Effects (*RiMUP*)*

- *Excessive gambling or other unusual urges such as increased sexual urges, binge or compulsive eating and compulsive shopping. If you or your family members notice that you are having unusual urges or behaviours, talk to your doctor or pharmacist.*

Tarikh pelaksanaan keperluan mengemaskini maklumat berkenaan pada semua produk farmaseutikal yang mengandungi aripiprazole adalah seperti berikut:

Permohonan baru dan produk dalam proses penilaian: **1 November 2017**
Produk berdaftar: **1 Mei 2018**

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

Tarikh kuat kuasa arahan ini adalah mulai **1 November 2017.**

3. DIREKTIF 23/17 [RUJ: (28) DLM. BPFK/PPP/07/25 JLD. 1]: KEMASKINI SISIP BUNGKUSAN DAN RiMUP DENGAN MAKLUMAT KESELAMATAN BERKAITAN INTERAKSI UBAT UNTUK SEMUA PRODUK FARMASEUTIKAL YANG MENGANDUNGI OPIOID DAN BENZODIAZEPIN

Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke-316 pada 3 Oktober 2017 telah membuat keputusan bagi semua produk farmaseutikal 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** untuk mengemaskini sisip bungkusan dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat keselamatan berkaitan interaksi ubat seperti berikut:

Warnings and Precautions (sisip bungkusan)

Risks from Concomitant Use with Benzodiazepines/ Opioids

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of <product name> with benzodiazepines/ 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 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/ opioids. Advice patients not to drive or operate heavy machinery until the effects of concomitant use of benzodiazepine/ opioids 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/ opioids (See Drug Interactions).

Drug Interactions (sisip bungkusan)

Benzodiazepines/ 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 the actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at the μ-receptors, and the benzodiazepines interact at the $GABA_A$ 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.

Taking other medicines (RiMUP)

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

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.

Tarikh pelaksanaan keperluan mengemaskini maklumat berkenaan pada semua produk farmaseutikal yang mengandungi opioid dan benzodiazepine adalah seperti berikut:

Permohonan baru dan produk dalam proses penilaian: **1 November 2017**
Produk berdaftar: **1 Mei 2018**

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

Tarikh kuat kuasa arahan ini adalah mulai **1 November 2017.**

4. DIREKTIF 24/17 [RUJ: (29) DLM. BPFK/PPP/07/25 JLD. 1]: KEMASKINI SISIP BUNGKUSAN DAN RiMUP DENGAN MAKLUMAT KESELAMATAN BERKAITAN RISIKO *SPONTANEOUS ABORTION* DAN *MULTIPLE CONGENITAL ABNORMALITIES* SERTA PENGGUNAAN DALAM KALANGAN IBU MENYUSU UNTUK SEMUA PRODUK FARMASEUTIKAL YANG MENGANDUNGI FLUCONAZOLE

Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke-316 pada 3 Oktober 2017 telah membuat keputusan bagi semua produk farmaseutikal yang mengandungi fluconazole untuk mengemaskini sisip bungkusan dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko *spontaneous abortion* dan *multiple congenital abnormalities* serta penggunaan dalam kalangan ibu menyusu seperti berikut:

Pregnancy and Lactation (sisip bungkusan)

Use During Pregnancy

There have been reports of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150mg of fluconazole as a single or repeated dose in the first trimester.

Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom <product name> may be used if the anticipated benefit outweighs the possible risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the fetus.

Effective contraceptive measures should be considered in women of childbearing potential and should continue throughout the treatment period and for approximately 1 week (5 to 6 half0lives) after the final dose.

There have been reports of multiple congenital abnormalities in infants whose mothers were treated with high-dose (400mg/day to 800mg/day) fluconazole therapy for coccidioidomycosis (an unapproved indication). The relationship between fluconazole use and these events is unclear. Adverse fetal effects have been seen in animals only at high-dose levels associated with maternal toxicity. There were no fetal effects at 5mg/kg or 10mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25mg/kg and 50mg/kg and high doses. At doses ranging from 80mg/kg (approximately 20-60 times the recommended human dose) to 320mg/kg, embryolethality in rats were increased and fetal abnormalities included wavy ribs, cleft palate and abnormal craniofacial ossification.

Case reports describe a distinctive and rare pattern of birth defects among infants whose mothers received high dose (400-800mg/day) fluconazole therapy during most or all of the first trimester of pregnancy. The features seen in these infants include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis and congenital heart disease.

Use during Lactation

Fluconazole is found in human breast milk at concentrations similar to plasma. Breast-feeding may be maintained after a single dose of 150mg fluconazole. Breast-feeding is not recommended after repeated use of high-dose fluconazole.

Before you use <product name> (RiMUP)

Inform your doctor if you have such conditions:

- *Pregnant or planning to become pregnant*
    - *<product name> may cause harm to your unborn baby. You should not take <product name> while you are pregnant unless your doctor has told you to. Inform your doctor if you are pregnant or planning to become pregnant.*
    - *If you are a woman of child-bearing potential, avoid becoming pregnant during treatment. Use effective contraception during treatment and for 1 week after treatment.*

- *Breast-feeding*
    - *<product name> is excreted in human breast milk, hence its use in nursing mothers is not recommended. However, breast-feeding may be maintained if you took a single dose of <product name> 150mg. Breast-feeding is not recommended after a high dose (more than 150mg) or repeated use of <product name>.*

Tarikh pelaksanaan keperluan mengemaskini maklumat berkenaan pada semua produk farmaseutikal yang mengandungi fluconazole adalah seperti berikut:

Permohonan baru dan produk dalam proses penilaian: **1 November 2017**
Produk berdaftar: **1 Mei 2018**

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

Tarikh kuat kuasa arahan ini adalah mulai **1 November 2017.**

5. DIREKTIF 25/17 [RUJ: (30) DLM. BPFK/PPP/07/25 JLD. 1]: KEMASKINI SISIP BUNGKUSAN DAN RiMUP DENGAN MAKLUMAT BERKAITAN RISIKO PENGGUNAAN METFORMIN DALAM KALANGAN PESAKIT *MODERATELY REDUCED KIDNEY FUNCTION* DAN AMARAN *LACTIC ACIDOSIS* UNTUK SEMUA PRODUK FARMASEUTIKAL YANG MENGANDUNGI METFORMIN

Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke-316 pada 3 Oktober 2017 telah membuat keputusan bagi semua produk farmaseutikal yang mengandungi metformin untuk mengemaskini sisip bungkusan dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat berkaitan risiko penggunaan metformin dalam kalangan pesakit *moderately reduced kidney function* dan amaran *lactic acidosis* seperti berikut:

Recommended Dosage (sisip bungkusan)

a) Produk bahan aktif tunggal yang mengandungi metformin sahaja

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

GFR mL/min	*Total maximum daily dose (to be divided into 2-3 daily doses)**	*Additional considerations*
60-89	*3000mg*	*Dose reduction may be considered in relation to declining renal function*
45-59	*2000mg*	*Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.*
30-44	*1000mg*	
<30	*-*	*Metformin is contraindicated.*

b) Produk kombinasi yang mengandungi metformin

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should be preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR <60ml/min. if no adequate strength of <product name> is available, individual monocomponents should be used instead of the fixed dose combination.

GFR mL/min	*Metformin*	*[other monocomponent]*
60-89	*Maximum dose is 3000mg. Dose reduction may be considered in relation to declining renal function*	
45-59	*Maximum dose is 2000mg. The starting dose is at most half of the maximum dose.*	
30-44	*Maximum dose is 1000mg. The starting dose is at most half of the maximum dose.*	
<30	*Metformin is contraindicated.*	

Contraindications (sisip bungkusan)

- *Severely reduced kidney function (GFR <30ml/min)*
- *Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)*

Warnings and Precautions (sisip bungkusan)

Lactic acidosis

Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a healthcare professional is recommended.

Medicinal that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia as well as concomitant use of medicinal products that may cause lactic acidosis.

Patients and caregivers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (<7.35), increased plasma lactate levels (>5mmol/L) and an increased anion gap and lactate/pyruvate ratio.

GFR should be assessed before initiation of treatment and regularly thereafter [see Recommended Dosage]. Metformin is contraindicated in patients with GFR <30ml/min and should be temporarily discontinued in the presence of conditions that alter renal function [see Contraindications].

Before you use <product name> (RiMUP)

Do not take <product name> :

- *If you have severely reduced kidney function.*
- *If you have lactic acidosis (too much lactic acid in the blood [see "Risk of lactic acidosis" below] or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms of acidosis may include stomach pain, abnormal breathing and drowsiness (if severe).*

Before you use start to use it: (RiMUP)

Risk of lactic acidosis

<Product name> may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration, liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease). If any of the above applies to you, talk to your doctor for further instructions.
Stop taking <product name> for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

Stop taking <product name> and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma. Symptoms include:

- *Vomiting*
- *Stomach ache*
- *Muscle cramps*
- *A general feeling of not being well with severe tiredness*
- *Difficulty in breathing*

During treatment with <product name>, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

Tarikh pelaksanaan keperluan mengemaskini maklumat berkenaan pada semua produk farmaseutikal yang mengandungi metformin adalah seperti berikut:

Permohonan baru dan produk dalam proses penilaian: **1 November 2017**
Produk berdaftar: **1 Mei 2018**

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

Tarikh kuat kuasa arahan ini adalah mulai **1 November 2017.**

6. DIREKTIF 26/17 [RUJ: (31) DLM. BPFK/PPP/07/25]: PINDAAN HAD HARIAN PENGAMBILAN MENTHOL DALAM PERSEDIAAN ORAL

Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke-317 pada 30 Oktober 2017 telah membuat keputusan meminda had harian pengambilan menthol dalam persediaan oral kepada *0.4mg/kg body weight/day (dosage and use in children should be clearly stated).* Keperluan ini telah dikemaskini pada *Drug Registration Guidance Document (DRGD), Section 8.2.2 List of Restricted Excipients.*

Keperluan ini hanya perlu dipatuhi bagi permohonan pendaftaran produk baharu yang dikemukakan selepas tarikh kuatkuasa direktif ini. Tarikh kuatkuasa direktif ini adalah mulai **1 Januari 2018.**

7. DIREKTIF 27/17 [RUJ: (32) DLM. BPFK/PPP/07/25]: KEMASKINI SISIP BUNGKUSAN DAN RiMUP DENGAN MAKLUMAT KESELAMATAN BERKAITAN INTERAKSI UBAT DAN RISIKO ADVERS *ADRENAL INSUFFICIENCY* DAN *ANDROGEN DEFICIENCY* KESAN PENGGUNAAN JANGKA PANJANG UNTUK SEMUA PRODUK FARMASEUTIKAL YANG MENGANDUNGI OPIOID

Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke-318 pada 27 November 2017 telah membuat keputusan bagi semua produk farmaseutikal yang mengandungi opioid untuk mengemaskini sisip bungkusan dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat berkaitan interaksi ubat dan risiko advers *adrenal insufficiency* dan *androgen deficiency* kesan penggunaan jangka panjang seperti berikut:

Warnings and Special Precautions (sisip bungkusan)

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 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. 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 Post-marketing Experience].

Undesirable Effects/Side Effects (sisip bungkusan)

Post-marketing 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 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 reproductive potential. It is not known whether these effects on fertility are reversible.*

Undesirable Effects/Side Effects (sisip bungkusan)

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 serotonin 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].

While you are using <product name> (RiMUP)

Things to be careful of:

- *Serotonin syndrome: <product name> may cause a rare but potentially life-threatening condition resulting from a 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 potential 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.*

Tarikh pelaksanaan keperluan mengemaskini maklumat berkenaan pada semua produk farmaseutikal yang mengandungi opioid adalah seperti berikut:

Permohonan baru dan produk dalam proses penilaian: **1 Januari 2018**
Produk berdaftar: **1 Jun 2018**

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

Tarikh kuat kuasa arahan ini adalah mulai **1 Januari 2018.**

8. DIREKTIF 28/17 [RUJ: (33) DLM. BPFK/PPP/07/25 JLD. 1]: KEMASKINI SISIP BUNGKUSAN DAN RiMUP BAGI SEMUA PRODUK YANG MENGANDUNGI AZITHROMYCIN DAN ERYTHROMYCIN KECUALI PERSEDIAAN TOPIKAL/EKSTERNAL/MATA DENGAN AMARAN BERKAITAN RISIKO *INFANTILE HYPERTROPHIC PYLORIC STENOSIS* (IHPS)

Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke-318 pada 27 November 2017 telah membuat keputusan bagi semua produk yang mengandungi azithromycin dan erythromycin kecuali persediaan topikal/eksternal/mata untuk mengemaskini sisip bungkusan dan risalah maklumat ubat untuk pengguna (RiMUP) dengan amaran berkaitan risiko *Infantile Hypertrophic Pyloric Stenosis* (IHPS) seperti berikut:

Warnings and Special Precautions for Azithromycin (sisip bungkusan)

Infantile Hypertrophic Pyloric Stenosis (IHPS) has been reported following the use of azithromycin in infants(treatment up to 42 days of life). Parents and caregivers should be informed to contact their physician if vomiting and/or irritability with feeding occurs.

Warnings and Special Precautions for Erythromycin (sisip bungkusan)

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occuring in infants following erythromycin therapy. In one cohort of 157 newborns who were given erythromycin for pertussis prophylaxis, seven neonates (5%) developed symptoms of non-bilious vomiting or irritability with feeding and were subsequently diagnosed as having IHPS requiring surgical pyloromyotomy. Since erythomycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or chlamydia), the benefit of erythromycin therapy needs to be weighed against potential risk of developing IHPS. Parents and caregivers should be informed to contact their physician if vomiting and/or irritability with feeding occurs.

Undesirable Effects/Side Effects for Azithromycin/Erythromycin (sisip bungkusan)

Post-marketing Experience
Gastrointestinal Disorders: infantile hypertrophic pyloric stenosis

Side Effects for Azithromycin/Erythromycin (RiMUP)

If you notice that the child vomits and/or irritability with feeding occurs, contact your doctor immediately as it may be due to the Infantile Hypertrophic Pyloric Stenosis (IHPS).

Tarikh pelaksanaan keperluan mengemaskini maklumat berkenaan adalah seperti berikut:

Permohonan baru dan produk dalam proses penilaian: **1 Januari 2018**
Produk berdaftar: **1 Jun 2018**

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

Tarikh kuat kuasa arahan ini adalah mulai **1 Januari 2018.**

9. DIREKTIF 29/17 [RUJ: (34) DLM. BPFK/PPP/07/25 JLD. 1]: KEMASKINI SISIP BUNGKUSAN DAN RiMUP BAGI SEMUA PRODUK YANG MENGANDUNGI STATIN DENGAN MAKLUMAT BERKAITAN *IMMUNE-MEDIATED NECROTIZING MYOPATHY (IMNM)*

Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke-318 pada 27 November 2017 telah membuat keputusan bagi semua produk yang mengandungi statin untuk mengemaskini sisip bungkusan dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat berkaitan *Immune-mediated Necrotizing Myopathy (IMNM)* seperti berikut:

Warnings and Special Precautions (sisip bungkusan)

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by:

- *Persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment*
- *Muscle biopsy showing necrotizing myopathy without significant inflammation*
- *Improvement with immunosuppressive agents.*

Undesirable Effects/Side Effects (sisip bungkusan)

Musculoskeletal disorder
Frequently not known: Immune-mediated Necrotizing Myopathy.

Side Effects (RiMUP)

If you have muscle problems that do not go away even after your doctor has told you to stop taking <product name>, please refer to your doctor. Your doctor may do further tests to diagnose the cause of your muscle problems.

Tarikh pelaksanaan keperluan mengemaskini maklumat berkenaan pada semua produk farmaseutikal yang mengandungi statin adalah seperti berikut:

Permohonan baru dan produk dalam proses penilaian: **1 Januari 2018**
Produk berdaftar: **1 Jun 2018**

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

Tarikh kuat kuasa arahan ini adalah mulai **1 Januari 2018.**

SIARAN AKHBAR

KENYATAAN AKHBAR KETUA PENGARAH KESIHATAN: PRODUK-PRODUK KOSMETIK YANG DIKESAN MENGANDUNGI RACUN BERJADUAL

Bahagian Regulatori Farmasi Negara (NPRA), Kementerian Kesihatan Malaysia (KKM) ingin menggesa orang awam untuk mengelak daripada membeli dan menggunakan produk-produk kosmetik berikut kerana dikesan mengandungi racun berjadual seperti di bawah:

Nama Produk	No. Notifikasi	Racun Berjadual yang dikesan	Nama Pemegang Notifikasi
Nuriz Shoppe -Uv Pearl Cream	NOT150900193K	Merkuri	Progressive Mix Industries
Nuriz- D'solve	NOT150900191K	Merkuri	Progressive Mix Industries
Aura Gorgeous Night Cream	NOT151204804K	Merkuri	Aura Gorgeous Beauty & Healthy
NV Anti Blemish Toner 1	NOT140304146K	Hydroquinone dan Tretinoin	Nouvelle Beauty Centre Sdn. Bhd.

Notifikasi produk-produk kosmetik terlibat telah dibatalkan oleh Pengarah Kanan Perkhidmatan Farmasi, KKM berikutan pengesanan bahan racun berjadual di dalam produk berkenaan.

Produk yang mengandungi **hydroquinone dan tretinoin** adalah merupakan produk farmaseutikal yang perlu berdaftar dengan Pihak Berkuasa Kawalan Dadah (PBKD) dan hanya boleh digunakan dengan nasihat profesional kesihatan.

Produk kosmetik yang dicampurpalsu dengan **hydroquinone** boleh menyebabkan kemerahan pada kulit yang disapu, ketidakselesaan, perubahan warna kulit yang tidak diingini, malah kulit menjadi hipersensitif. Kesan daripada penggunaan hydroquinone boleh menghalang proses pigmentasi (depigmentasi) yang mengurangkan perlindungan kulit daripada pancaran sinar UV merbahaya dan boleh meningkatkan risiko kanser kulit.

Produk kosmetik yang dicampurpalsu dengan **tretinoin** biasanya dipromosikan untuk tujuan merawat masalah jerawat dan membantu mengurangkan kedutan. Penggunaan tretinoin tanpa pengawasan boleh menyebabkan bahagian kulit yang disapu menjadi kemerahan, tidak selesa, pedih, mengelupas dan hipersensitif kepada cahaya matahari.

Nama Produk	Gambar Produk	Nama Produk	Gambar Produk
Nuriz Shoppe -Uv Pearl Cream		Aura Gorgeous Night Cream	
Nuriz-D'solve		NV Anti Blemish Toner 1	

Produk kosmetik yang dicampurpalsu dengan **merkuri** boleh memudaratkan kesihatan kerana merkuri yang terkandung dalam produk kosmetik boleh menyerap masuk ke dalam badan dan menyebabkan kerosakan pada buah pinggang dan sistem saraf. Ia juga boleh menganggu perkembangan otak kanak-kanak yang masih kecil atau yang belum dilahirkan.

Selain itu, kesan mudarat akibat pendedahan kepada merkuri boleh juga dialami oleh orang sekeliling terutamanya kanak-kanak apabila produk kosmetik yang mengandungi merkuri yang disapu pada kulit meruap dan dihidu. Bayi dan kanak-kanak kecil boleh terdedah kepada merkuri apabila mereka menyentuh produk kosmetik yang mengandungi merkuri atau orang yang menggunakan produk kosmetik tersebut dan kemudiannya memasukkan jari-jari mereka ke dalam mulut. Penggunaan produk yang mengandungi merkuri boleh juga menyebabkan ruam, iritasi dan perubahan lain pada kulit.

PERINGATAN KEPADA PENJUAL DAN PENGEDAR PRODUK KOSMETIK

Penjual dan pengedar produk-produk kosmetik ini diberi amaran untuk menghentikan penjualan dan pengedaran produk-produk kosmetik tersebut dengan serta-merta. Penjual adalah diingatkan bahawa penjualan dan pengedaran produk-produk kosmetik ini adalah melanggar Peraturan Peraturan Kawalan Dadah dan Kosmetik 1984.

Individu yang melakukan kesalahan di bawah Peraturan-Peraturan ini boleh dikenakan hukuman denda tidak melebihi RM25,000 atau penjara tidak melebihi 3 tahun atau kedua-duanya untuk kesalahan pertama dan denda tidak melebihi RM50,000 atau penjara tidak melebihi 5 tahun atau kedua-duanya untuk kesalahan-kesalahan berikutnya. Syarikat yang melakukan kesalahan boleh dikenakan denda sehingga RM50,000 untuk kesalahan pertama dan denda sehingga RM100,000 untuk kesalahan berikutnya.

Sebarang pertanyaan berkaitan produk kosmetik boleh diemel kepada kosmetik@npra.gov.my atau menghubungi talian 03-78835400. Semakan status notifikasi kosmetik di laman web http://npra.moh.gov.my

DIREKTORI NPRA

Bahagian Regulatori Farmasi Negara (NPRA)	+ 603 - 7883 5400
PUSAT	**NO. SAMBUNGAN**
Pusat Pendaftaran Produk – Pejabat Timbalan Pengarah	5511
• Seksyen Bahan Aktif Farmaseutikal	5489
• Seksyen Bioteknologi	8424
• Seksyen Ubat Komplementari	5523
• Seksyen Ubat Generik	5497
• Seksyen Ubat Baru (NCE)	8429
• Seksyen Ubat Veterinar	5500
• Seksyen Koordinasi Regulatori	8423
Pusat Pasca Pendaftaran Produk & Kawalan Kosmetik- Pejabat Timbalan Pengarah	5538
• Seksyen Kosmetik	5532
• Seksyen Farmakovigilan	8470
• Seksyen Surveilan dan Aduan Produk	5543
Pusat Kajian Produk Baru– Pejabat Timbalan Pengarah	5581
• Seksyen Penilaian Produk Kajian	8406
• Seksyen Keselamatan Produk Kajian	8405
• Seksyen *Good Laboratory Practice (GLP)*	8404
• Seksyen *Good Clinical Practice (GCP)*	8401
• Seksyen Pusat Kajian Bioekuivalens & JK Etika	8403
Pusat Komplians & Perlesenan– Pejabat Timbalan Pengarah	5580
• Seksyen Amalan Perkilangan Baik 1	5569
• Seksyen Amalan Perkilangan Baik 2	5577
• Seksyen Amalan Perkilangan Baik 3	5567
• Seksyen Amalan Edaran Baik	8562
• Seksyen Perlesenan	5566
• Seksyen Amalan Kualiti & Pensijilan	5573
Pusat Pembangunan & Perancangan Strategik– Pejabat Timbalan Pengarah	5553
• *Helpdesk*	5560, 5561, 5562
• Seksyen Koordinasi Kualiti, Kompetensi & Komunikasi	8481
• Seksyen Koordinasi ICT	5555
Pusat Kawalan Kualiti– Pejabat Timbalan Pengarah	5429
• Seksyen Pengujian Biofarmaseutikal	8490
• Seksyen Pengujian Ubat Komplementari	8892
• Seksyen Pengujian Kimia Farmaseutikal	8894
• Seksyen Penyelidikan	8446
• Seksyen Piawai Rujukan	5468
• Seksyen Perkhidmatan Makmal	5431
Pusat Pentadbiran	5412

BAHAGIAN REGULATORI FARMASI NEGARA (NPRA), KEMENTERIAN KESIHATAN MALAYSIA
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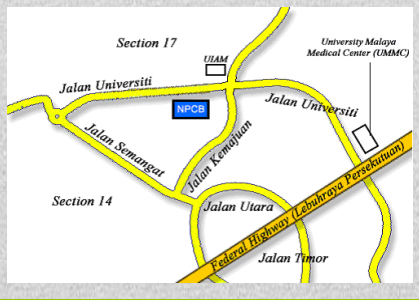

Laman Web: http://npra.moh.gov.my