KEMENTERIAN KESIHATAN MALAYSIA
(*Ministry of Health Malaysia*)
Bahagian Regulatori Farmasi Negara (NPRA)
Lot 36, Jalan Universiti
46200 Petaling Jaya
Selangor
MALAYSIA

No. Telefon : 03 - 7883 5400
No. Faksimili : 03 - 7956 2924
Portal Rasmi : http://npra.moh.gov.my
E-mel Rasmi : npra@npra.gov.my

Ruj. Kami: (12) dlm. BPFK/PPP/07/25 Jld. 3
Tarikh : 19 JUL 2019

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 12 TAHUN 2019: DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI ANTIBIOTIK KUMPULAN FLUOROQUINOLONE (SEDIAAN ORAL DAN INJEKSI): PENGEMASKINIAN SISIP BUNGKUSAN DAN RISALAH MAKLUMAT UBAT UNTUK PENGGUNA (RiMUP) DENGAN MAKLUMAT KESELAMATAN BERIKUT:

a) **MEMBATALKAN DAN MENGHADKAN INDIKASI ANTIBIOTIK KUMPULAN FLUOROQUINOLONE**
b) **AMARAN BERKAITAN *DISABLING AND POTENTIALLY PERMANENT SIDE EFFECTS (TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY & CENTRAL NERVOUS SYSTEM/ NEUROPSYCHIATRIC EFFECTS)***

Adalah saya merujuk kepada Arahan Bilangan 12 Tahun 2019 oleh Pengarah Kanan Perkhidmatan Farmasi.

2. Dimaklumkan bahawa Pengarah Kanan Perkhidmatan Farmasi, Kementerian Kesihatan Malaysia dalam Arahan Bilangan 12 Tahun 2019 telah bersetuju untuk menambah maklumat keselamatan bagi semua produk yang mengandungi antibiotik kumpulan fluoroquinolone (sediaan oral dan injeksi) seperti pada surat arahan Bil.(12) BPFK/PPP/07/25 Jld.3 seperti berikut:

i. Membatalkan dan menghadkan indikasi antibiotik kumpulan fluoroquinolone
ii. Amaran berkaitan *disabling and potentially permanent side effects (tendinitis, tendon rupture, peripheral neuropathy & central nervous system/neuropsychiatric effects)*

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

Sekian, terima kasih.

"BERKHIDMAT UNTUK NEGARA"

Saya yang menjalankan amanah,

(DATIN DR. FARIDAH ARYANI BINTI MD. YUSOF) **RPh 1197**
Pengarah
Bahagian Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia

AAG/nb/ppp/NPRA/100719
AAG/nb
azizahag@npra.gov.my/ nurhidayah@npra.gov.my
+603 – 7883 5521/5526
+603 - 7958 1312

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

BILANGAN 12 TAHUN 2019

PENGEMASKINIAN SISIP BUNGKUSAN DAN RISALAH MAKLUMAT UBAT UNTUK PENGGUNA (RiMUP) BAGI SEMUA PRODUK YANG MENGANDUNGI ANTIBIOTIK KUMPULAN FLUOROQUINOLONE DALAM FORMULASI SISTEMIK (TERMASUK DOS SEDIAAN ORAL DAN INJEKSI) DENGAN MAKLUMAT KESELAMATAN BERIKUT:

(i) MEMBATALKAN DAN MENGHADKAN INDIKASI ANTIBIOTIK KUMPULAN FLUOROQUINOLONE

(ii) AMARAN BERKAITAN *DISABLING AND POTENTIALLY PERMANENT SIDE EFFECTS (TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY & CENTRAL NERVOUS SYSTEM/NEUROPSYCHIATRIC EFFECTS)*

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 antibiotik kumpulan fluoroquinolone dalam formulasi sistemik (termasuk dos sediaan oral dan injeksi) bagi mengemaskini sisip bungkusan dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat keselamatan berikut:

(i) Membatalkan dan menghadkan indikasi antibiotik kumpulan fluoroquinolone

(ii) Amaran berkaitan disabling and potentially permanent side effects (*tendinitis, tendon rupture, peripheral neuropathy & central nervous system/neuropsychiatric effects*)

LATAR BELAKANG

2.1 Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke **336** pada **4 Julai 2019** telah membuat keputusan bagi semua produk yang mengandungi antibiotik kumpulan fluoroquinolone dalam formulasi sistemik (termasuk dos sediaan oral dan injeksi) bagi mengemaskini sisip bungkusan dan risalah maklumat ubat untuk pengguna (RiMUP) dengan maklumat keselamatan berikut:

(i) Membatalkan dan menghadkan indikasi antibiotik kumpulan fluoroquinolone

(ii) Amaran berkaitan *disabling and potentially permanent side effects* (*tendinitis, tendon rupture, peripheral neuropathy & central nervous system/neuropsychiatric effects*)

PELAKSANAAN

3.1 Oleh itu arahan – arahan berikut perlu dipatuhi untuk semua produk yang mengandungi antibiotik kumpulan fluoroquinolone dalam formulasi sistemik (termasuk dos sediaan oral dan injeksi) seperti berikut:-

3.1.1 Sisip bungkusan

Pada bahagian *Indication:*

(i) *The following statement should be included:*

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

(ii) The following indication(s), if relevant, should be deleted:

- *Acute bronchitis*
- *Laryngitis*
- *Pharyngitis-tonsillitis*
- *Prophylaxis of infectious gastroenteritis / traveller's diarrhoea*

- *Selective decontamination of gastrointestinal tract in patients with compromised immune system*
- *Vaginal infections*

(iii) The following indication(s), if relevant, should be restricted:

- *Acute bacterial rhinosinusitis**
- *Acute exacerbation of chronic obstructive pulmonary disease including chronic bronchitis**
- *Nosocomial pneumonia / Hospital-acquired pneumonia**
- *Acute otitis media**
- *External otitis**
- *Endocarditis**
- *Infection of cerebrospinal fluid**
- *Meningitis**
- *Septicaemia**
- *Uncomplicated acute cystitis / uncomplicated cystitis**
- *Prevention of exacerbations in women with recurring urinary tract infections**
- *Prevention of infection in surgical procedures in the urogenital system*,#*
- *Pre-operative preparations for chronic cholesteatomatous otitis and chronic otitis spreading to bone**

(iv) The following text should be added after the restricted indications in part (iii):

*<Product name> should be only used :

- *When Pseudomonas is considered AND the patient is allergic to antipseudomonal penicillins/cephalosporins;*
- *For resistant organisms with no other alternative antibiotics available.*

#*<Product name> should not be used >24 hours post operation.*

Pada bahagian *Warnings and Precautions:*

The use of [INN] should be avoided in patients who have experienced serious adverse reactions in the past when using fluoroquinolones containing products (see section Adverse Effects/Undesirable Effects). Treatment of these patients with [INN] should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

Prolonged, disabling and potentially irreversible serious adverse drug reactions
Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving fluoroquinolones irrespective of their age and pre-existing risk factors. [INN] should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Tendinitis and tendon rupture
Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients (above 60 years of age), with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.*

At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with [INN] should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

**[For systemically administered levofloxacin-containing products, the listing of risk factors should additionally include: "in patients receiving daily doses of 1000 mg levofloxacin".]*

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with [INN] should be advised to inform their doctor and pharmacist prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see section Adverse Effects/Undesirable Effects).

Pada bahagian *Adverse Effects/Undesirable Effects:*

*Musculoskeletal and connective tissue disorders**
*Nervous system disorders**
*General disorders and administrative site conditions**
*Psychiatric disorders**
*Eye disorders**
*Ear and labyrinth disorders**

**Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of fluoroquinolones in some cases irrespective of pre-existing risk factors (see section Warnings and Precautions).*

3.1.2 Risalah Maklumat Ubat Untuk Pengguna (RiMUP)

Pada bahagian *Before you use <product name>:*

Before you start to use it:

You should not take fluoroquinolone antibacterial medicines, including <product name>, if you have experienced any serious adverse reaction in the past when taking a fluoroquinolone (see section Things to be careful of and Side effects). In this situation, you should inform your healthcare providers as soon as possible.

Pada bahagian *While you are using it:*

Things to be careful of:

Prolonged, disabling and potentially irreversible serious side effects

Fluoroquinolone antibacterial medicines, including <product name>, have been associated with very rare but serious side effects, some of them being long lasting (continuing months or years), disabling or potentially irreversible.

Stop taking your fluoroquinolone antibiotic and contact your healthcare providers immediately if you have the following signs of a side effect:

- *Tendon pain or swelling, often beginning in the ankle or calf. If this happens, rest the painful area until you can see your healthcare providers.*
- *Pain in your joints or swelling in your shoulder, arms, or legs.*
- *Abnormal pain or sensations (such as persistent pins and needles, tingling, tickling, numbness, or burning), weakness in your body, especially in the legs or arms, or difficulty walking.*
- *Severe tiredness, depressed mood, anxiety, problems with your memory, or severe problems sleeping.*
- *Changes in your vision, taste, smell, or hearing.*

Tell your healthcare providers if you have had one of the above effects during or shortly after taking a fluoroquinolone – this means you should avoid them in the future. You and your healthcare providers will decide on continuing the treatment considering also an antibiotic from another class.

Tendinitis and tendon rupture

Pain and swelling in the joints and inflammation or rupture of tendons may occur rarely. Your risk is increased if you are elderly (above 60 years of age), have received an organ transplant, have kidney problems or if you are being treated with corticosteroids. Inflammation and ruptures of tendons may occur within the first 48 hours of treatment and even up to several months after stopping of <product name> therapy. At the first sign of pain or inflammation of a tendon (for example in your ankle, wrist, elbow, shoulder or knee), stop taking <product name>, contact your healthcare providers and rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.

Peripheral neuropathy

You may rarely experience symptoms of nerve damage (neuropathy) such as pain, burning, tingling, numbness and/or weakness especially in the feet and legs or hands and arms. If this happens, stop taking <product name>

and inform your healthcare providers immediately in order to prevent the development of potentially irreversible condition.

Pada bahagian *Side effects:*

Fluoroquinolones have been reported to cause serious side effects involving tendons, muscles, joints, and the nerves – in a small proportion of patients, these side effects caused long-lasting or permanent disability (see section Before you start to use it and Things to be careful of).

4. Tarikh pelaksanaan keperluan mengemaskini maklumat berkenaan pada semua produk yang mengandungi antibiotik kumpulan fluoroquinolone dalam formulasi sistemik (termasuk dos sediaan oral dan injeksi) termasuk kombinasi bagi:

(a) Permohonan baru dan produk yang sedang dalam proses penilaian : **1 Ogos 2019**

(b) Produk berdaftar : **1 Februari 2020**

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 Ogos 2019.**

"BERKHIDMAT UNTUK NEGARA"

(DR. RAMLI BIN ZAINAL) RPh. 1045
Pengarah Kanan Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia

AAG/nb/ppp/NPRA/100719

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

2. Pengarah
Bahagian Amalan dan Perkembangan Farmasi
Kementerian Kesihatan Malaysia

3. Pengarah
Bahagian Penguatkuasaan Farmasi
Kementerian Kesihatan Malaysia