Newsletter of the Drug Control Authority, Malaysia

BERITA UBAT-UBATAN

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EVENT

PUBLIC SECTOR CONDUCIVE ECOSYSTEM (EKSA) CERTIFICATION BY MAMPU

The National Pharmaceutical Control Bureau (NPCB) was successfully assessed by 2 assessors from the Malaysian Administrative Modernisation and Management Planning Unit (MAMPU), Puan Rasidah Ibrahim and Puan Hemalatha A/P Suppiah on the 27th - 28th November 2014.

The introduction of EKSA is meant to enhance the existing Public Sector 5S Practice with an emphasis on creating a conducive working environment. This move is in line with efforts to strengthen the organisational culture of high performance and innovation among public sector agencies by providing a conducive environment, work culture and positive values for public servants.

The rebranding is aimed at empowering public sector agencies to:

- enhance their corporate image;
- promote efforts supporting the campaign to Go Green;
- inculcate a culture of creativity and innovation in line with stakeholder expectations;
- expand the implementation of the Public Sector Conducive Ecosystem among public sector agencies; and
- ensure that auditing elements meet the needs of various public sector agencies.

IN THIS ISSUE

DCA EDITORIAL TEAM

NEW DIRECTIVES

The following directives have been issued under Regulation 29 of the Control of Drugs and Cosmetics Regulations 1984 (Revised 2006) by the Senior Director of Pharmaceutical Services, YBhg. Dato' Eisah A. Rahman.

Directives 07/14 - 13/14 were issued following the decision made by the Drug Control Authority (DCA) in its 279th Meeting on 28th August 2014, that will take effect **according to these dates**:

The package insertsupdating process:
New registration and products under evaluation:**1st October 2014**
Registered products: **Six (6) months from 1st October 2014**

The application for amendments of package inserts must be done through variation application.

These directives will take effect from **1st October 2014.**

1. ***Directive 07/14[Ruj: (14) dlm. BPFK/PPP/07/25]: Enforcement of Warnings Regarding the Risk of Cognitive Adverse Effects and Increases in HbA1c and Fasting Blood Glucose (FBG) for All Statin Products***

Following the decision made by the Drug Control Authority (DCA) in its 279thMeeting on 28th August 2014, thisdirective was issued **to enforce warnings on the risk of cognitive adverse effects and increases in HbA1c and fasting blood glucose (FBG) for all statin products**.

Therefore, the following instructions must be adhered to for **all statin products** (single active ingredient or combination products) including atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin:

Undesirable Effects:

There have been rare post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median 3 weeks).

Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

2. ***Directive 08/14 [Ruj: (15) dlm. BPFK/PPP/07/25]: Restriction on Dosage of all Pravastatin Products to Reduce Risk of Muscle Injury***

A directive was issued following the decision made by the Drug Control Authority (DCA) in its 279th meeting on 28th August 2014 to **restrict the dosage of pravastatin** in order to reduce the risk of muscle injury for all products containing pravastatin.

Therefore, the following instructions must be adhered to for **all products containing pravastatin:**

Dosage and Administration:

Dosage in Patients Taking Cyclosporine

In patients taking cyclosporine, with or without other immunosuppressive drugs, concomitantly with [Product Name], therapy should be initiated with 10mg/day and titration to higher doses should be performed with caution. Most patients treated with this combination received a maximum pravastatin dose of 20mg/day.

Warning and Precautions:

Skeletal Muscle Effects

The use of fibrates alone may occasionally be associated with myopathy. The benefit of further alterations in lipid levels by the combined use of [Product Name] with fibrates should be carefully weighed against the potential risks of this combination.

Cases of myopathy, including rhabdomyolysis, have been reported with pravastatin co-administered with colchicine, and caution should be exercised when prescribing pravastatin with colchicine.

Pravastatin must not be co-administered with systemic fusidic acid. There have been reports of rhabdomyolysis (including some facilities) in patients receiving this combination. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Pravastatin therapy may be re-introduced seven days after the last dose of fusidic acid.

Interactions:

Concomitant Therapy with Other Lipid Metabolism Regulators: Based on post-marketing surveillance, gemfibrozil, fenofibrate, other fibrates and lipid lowering doses of niacin (nicotinic acid) may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. Therefore, combined drug therapy should be approached with caution.

Gemfibrozil and nicotinic acid: Gemfibrozil and nicotinic acid do not statistically significantly affect the bioavailability of pravastatin. However, in a limited size clinical trial, a trend toward CK elevations and musculoskeletal symptoms was seen in patients treated concurrently with pravastatin and gemfibrozil. Myopathy, including rhabdomyolysis, has occurred in patients who were receiving coadministration of HMG-CoA reductase inhibitors with fibric acid derivatives and niacin, particularly in subjects with pre-existing renal insufficiency.

Cyclosporine: In a multicentre study, the AUC values of pravastatin were shown to be five-fold higher in the presence of cyclosporine. There was no accumulation of pravastatin after multiple doses.

Clarithromycin, colchicine: The risk of myopathy/rhabdomyolysis is increased with concomitant administration of clarithromycin or colchicine with pravastatin.

Fusidic acid: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of pravastatin with systemic fusidic acid. Co-administration of this combination may cause increased plasma concentrations of both agents. The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with fusidic acid is necessary, pravastatin treatment should be discontinued throughout the duration of the fusidic acid treatment.

3. Directive 09/14 [Ruj: (16) dlm. BPFK/PPP/07/25]: Restriction on Dosage of Rosuvastatin to Reduce Risk of Muscle Injury

A directive was issued following the decision made by the Drug Control Authority (DCA) in its 279th meeting on 28th August 2014 to **restrict the dosage of rosuvastatin** in order to reduce the risk of muscle injury for all products containing rosuvastatin.

Therefore, the following instructions must be adhered to for **all products containing rosuvastatin:**

Dosage and Administration:

Dosage in patients with pre-disposing factors to myopathy
The recommended start dose is 5mg in patients with pre-disposing factors to myopathy.

Concomitant Therapy
Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when rosuvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir). Whenever possible, alternative medications should be considered, and if necessary, consider temporarily discontinuing [Product Name] therapy. In situations where co-administration of these medicinal products with rosuvastatin is unavoidable, the benefit and the risk of concurrent treatment and rosuvastatin dosing adjustments should be carefully considered.

Contraindications:

[Product Name] is contraindicated in patients receiving concomitant cyclosporine.

Warning and Precautions:

Skeletal Muscle Effects
Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations.

Updating the package insert of all generic products containing rosuvastatin mustinclude all areas related to safety issues. This involves updated information in the package insert of innovator products for example in the **Interactions, Pharmacokinetics** and other parts related.

4. Directive 10/14 [Ref: (17) dlm. BPFK/PPP/07/25]: Restriction on Dosage of Atorvastatin to Reduce Risk of Muscle Injury

A directive was issued following the decision made by the Drug Control Authority (DCA) in its 279th meeting on 28th August 2014 to **restrict the dosage of atorvastatin** in order to reduce the risk of muscle injury for all products containing atorvastatin.

Therefore, the following instructions must be adhered to for **all products containing atorvastatin:**

Dosage and Administration:

Dosage in Patients Taking Cyclosporine , Clarithromycin, Itraconazole, or Certain Protease Inhibitors
In patients taking cyclosporineor the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with [Product Name] should be avoided.

In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing [Product Name] and the lowest dose necessary employed.

In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with [Product Name]should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed.

In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with [Product Name] should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed.

Warning and Precautions:

Skeletal Muscle Effects

Physicians considering combined therapy with atorvastatin and fibrates, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin (≥ 1 g/day) should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Therefore, lower starting and maintenance doses of atorvastatin should also be considered when taken concomitantly with the aforementioned drugs. Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy.

Updating the package insert of all generic products containing atorvastatin mustinclude all areas related to safety issues. This involves updated information in the package insert of innovator products for example in the **Interactions, Pharmacokinetics** and other relatedparts.

5. Directive 11/14 [Ref: (18) dlm. BPFK/PPP/07/25]: Directive for All Products Containing Temozolomide – New Safety Information Regarding Risk of Hepatic Injury

A directive was issued following the decision made by the Drug Control Authority (DCA) in its 279th meeting on 28th August 2014 to **include new safety information regarding risk of hepatic injury for all products containing temozolomide.**

Therefore, the following instructions must be adhered to for **all products containing temozolomide:**

Warnings and Precautions:

Hepatic injury, including fatal hepatic failure has been reported in patients receiving temozolomide. Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure.

For patients on a 42 day treatment cycle, liver function test should be repeated midway during this cycle. For all patients, liver function test should be checked after each treatment cycle. For patients with significant liver function abnormalities, physicians should assess the benefit/risk of continuing treatement. Liver toxicity may occur several several weeks or more after the last treatment of temozolomide.

Side Effects:

Hepatic injury, including fatal hepatic failure has been reported.

Updating the package insert of all generic products containing atorvastatin mustinclude all areas related to safety issues. This involves updated information in the package insert of innovator products for example in the **Special Warnings and Precautions for Use, Adverse Effects** and other relatedparts.

6. *Directive 12/14 [Ref: (19) dlm. BPFK/PPP/07/25]: Directive for All Products Containing Methylphenidate – Warning on Risk of Priapism(Prolonged Erection Of The Penis) Among Men*

A directive was issued following the decision made by the Drug Control Authority (DCA) in its 279th meeting on 28th August 2014 to **include warning regarding risk of priapism (prolonged erection of the penis) among men for all products containing methylphenidate.**

Therefore, the following instructions must be adhered to for **all products containing methylphenidate:**

Warnings and Precautions:

Hepatic injury, including fatal hepatic failure has been reported in patients receiving temozolomide. Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure.

For patients on a 42 day treatment cycle, liver function test should be repeated midway during this cycle. For all patients, liver function test should be checked after each treatment cycle. For patients with significant liver function abnormalities, physicians should assess the benefit/risk of continuing treatement. Liver toxicity may occur several several weeks or more after the last treatment of temozolomide.

Side Effects:

Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

7. ***Directive 13/14 [Ref: (20) dlm. BPFK/PPP/07/25]: Directive for All Products Containing Filgrastim and Pegfilgrastim – Warning on Risk of Capillary Leak Syndrome (CLS) Among Cancer Patients and Healthy Donor (Filgrastim); and Cancer Patients (Pegfilgrastim)***

A directive was issued following the decision made by the Drug Control Authority (DCA) in its 279th meeting on 28th August 2014 to **include warning regarding risk of Capillary Leak Syndrome (CLS) among cancer patients and healthy donor (filgrastim); and cancer patients (pegfilgrastim).**

Therefore, the following instructions must be adhered to for **all biosimilarproducts containing filgrastim:**

Warnings and Precautions:

Capillary leak syndromehas been reported after granulocyte-colony stimulating factor administration and is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

Undesirable Effects:

Clinical Trials

In Cancer Patients

Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly (≥1/1000 to <1/100) in cancer patients undergoing chemotherapy following administration of granulocyte colony stimulating factors.

In Normal Donors undergoing peripheral blood progenitor cell mobilization

Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported in healthy donors undergoing peripheral blood progenitor cell mobilization following administration of granulocyte colony stimulating factors.

Post Marketing

Vascular Disorders

Cases of capillary leak syndrome have been reported in the post marketing setting with granulocyte colony stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis.

8. *Directive 15/14 [Ref: (22) dlm. BPFK/PPP/07/25]: Directive for All Products Containing Topiramate – Warning on Risk of Visual Field Defects*

This directive was issued following the decision made by the Drug Control Authority (DCA) in its 282nd meeting on 4th December 2014 to **include warning regarding risk of visual field defects *for* all products containing topiramate.**

Therefore, the following instructions must be adhered to for **all products containing topiramate:**

The package insert update process must be done according to these dates:
New registration and products under evaluation:**1st January 2015**
Registered products:**1st July 2015**

The application for amendments of package inserts must be done through variation application.

This directive will take effect from **1st January 2015.**

Special Warnings and Precautions For Use:

Visual Field Defects
Visual field defects have been reported in patients receiving topiramate independent of elevated intraocular pressure. In clinical trials, most of these events were reversible following topiramate discontinuation, however some cases were not. In a large proportion of postmarketing case reports reversibility was unknown, but in cases where an outcome was reported, the majority were reversible. If visual problems occur at any time during topiramate treatment, consideration should be given to discontinuing the drug.

SUMMARY OF PRESS RELEASES

COSMETICS

a) Caution on Using Cosmetic Products Containing Scheduled Poisons

The public is advised to avoid buying and using the following cosmetic products:

No.	Product Name	Notification Number	Scheduled Poison Detected	Name of Product Notification Holder	Name of Manufacturer
1.	Yellow Cream (Krim Ku-Neng)	NOT120101719K	Hydroquinone	Seri Mh Ummi Sdn. Bhd	Yamni Industry, Malaysia.
2.	Dnars Magic Gold Foundation	NOT111001084K	Hydroquinone	Seri Mh Ummi Sdn. Bhd	Yamni Industry, Malaysia.
3.	SF PROTECT & PERFECT DAY CREAM	NOT130604475K	Mercury	SF Infinity Resources	SirehEmas Marketing Sdn. Bhd

The notifications of the above cosmetics have been cancelled following the detection of the scheduled poison, **hydroquinone** and heavy metal, **mercury**which are prohibited in cosmetic products. These products are no longer allowed to be sold in Malaysia.

Products Containing Hydroquinone

Products containing hydroquinone are classified as pharmaceutical products that require registration with the Drug Control Authority (DCA) and can only be used under the advice of a healthcare professional. Hydroquinone is commonly used for the skin in hyperpigmentation conditions. Unsupervised use of preparations containing hydroquinone and/or tretinoin may cause unwanted side-effects.

Cosmetic products adulterated with hydroquinone are typically marketed for skin lightening, as well as, to treat blemishes and uneven skin tone. Hydroquinone can cause skin redness, discomfort, skin discoloration, hypersensitivity and a gradual blue-black darkening of the skin. Hydroquinone inhibits the pigmentation process (depigmentation) which reduces the skin's ability to be protected from harmful UV rays, thus, increasing the risk of skin cancer.

Product Containing Mercury

Mercury is prohibited in cosmetic products due to its potential hazard on human health. Mercury compounds are readily absorbed through the skin on topical application and tend to accumulate in the body. Direct and prolonged exposure to mercury can cause damage to the brain, nervous system and kidneys. Usage of products containing mercury can also result in skin rashes, irritation and other changes to the skin.

The company responsible for placing the product in the market has been instructed to immediately halt the sale and supply of the product mentioned and remove all physical stocks from the market within 72 hours.

Any person who is in possession of this product is advised to immediately cease selling, distributing or using it. The possessionof this product is an offence under the Control of Drugs and Cosmetics Regulations 1984.

CONTACTS & MAP

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CENTRES	EXTENSION NO.
Centre for Product Registration – Deputy Director	5487
• Active Pharmaceutical Ingredient Section	8424
• Biotechnology Section	8423
• Complementary Medicine Section	8415
• Generic Medicine Section	5490
• New Drug Section	5522
• Regulatory Coordination Section	5502
• Veterinary Medicine Section	5500
Centre for Post-Registration of Products – Deputy Director	5538
• Cosmetic Section	5532
• Pharmacovigilance Section	5543
• Surveillance and Product Complaints Section	5552
Centre for Investigational New Product – Deputy Director	5581
• BE Centre & Ethics Committee Compliance Section	8403
• GCP Compliance Section	8401
• GLP Compliance Section	8404
• Investigational Product Evaluation Section	8406
• Investigational Product Safety Monitoring Section	8405
Centre for Compliance and Licensing – Deputy Director	5564
• GDP Section	5568
• GMP 1 Section	5566
• GMP 2Section	5567
• Licensing and Certification Section	5569
• Quality and Industry Development Section	8556
Centre for Organisational Development – Deputy Director	5553
• Helpdesk	5560, 5561, 5562
• Information and Communications Technology Section	5555
• Quality, Competency & Communication Coordination Section	8481
Centre for Quality Control – Deputy Director	5429
• Bio-Pharmaceutical Testing Section	8894
• Complementary Medicines Testing Section	8892
• Laboratory Services Section	5431
• Pharmaceutical Chemistry Testing Section	8490
• Reference Standard Section	5468
• Research Section	8446
Centre for Administration	8458

NATIONAL PHARMACEUTICAL CONTROL BUREAU (NPCB), MINISTRY OF HEALTH MALAYSIA

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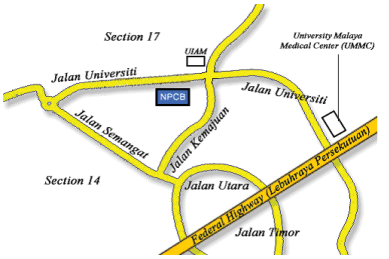

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