BERITA UBAT-UBATAN

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RESEARCH & DEVELOPMENT ABSTRACT

I ISOLATION, PURIFICATION AND STRUCTURAL DETERMINATION OF AN ANALOGUE OF TADALAFIL FOUND AS ADULTERANT IN HEALTH PRODUCT

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INTRODUCTION: The success of PDE5 inhibitors (sildenafil, tadalafil and vardenafil) in the treatment of erectile dysfunction has led to their widespread use as adulterants in herbal products, health dietary supplements and food. Consumption of adulterated products poses a serious health risk particularly the analogues since they have not been subjected to clinical trials and no safety and toxicity profiles available.

OBJECTIVE: The study was to isolate, purify and elucidate the structure of an analogue of tadalafil that has been reported to be used as adulterant.

METHODS: A product of specified adulterated candy was obtained from the enforcement unit and only 18 candies (a total of 76 g sample) were used. The adulterant was identified using TLC and HPLC, purified by gravity column chromatography and structural elucidation was done by FTIR and NMR. The study was carried out from July to November 2009.

RESULTS: The isolated and purified adulterant (130 mg or 0.17%) showed fairly similar molecular structure to that of tadalafil. The differences in the structure were confirmed using proton and carbon-13 NMR. Proton-proton and proton-carbon correlation was further highlighted using 2-D NMR. The evidence obtained from this study together with

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literature information concluded that the isolated adulterant is an analogue of tadalafil and was determined to be aminotadalafil. Purification process using gravity column chromatography was time consuming and skilled was required when packing the column. Adulterants are usually added in small quantities, therefore a bigger sample size is needed in order to isolate more compounds.

CONCLUSION: The method used was able to isolate, purify and subsequently determine the structure of an adulterant. This study has demonstrated that the isolation and purification method can be used as potential alternative for obtaining working standards from adulterated samples in the absence of reference materials.

Keyword: Isolation, purification, structural determination, analogue, adulterant, health product

II ISOLATION, PURIFICATION AND STRUCTURAL IDENTIFICATION OF AN ACETILDENAFIL ANALOGUE IN HERBAL PRODUCT

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INTRODUCTION/BACKGROUND: Some herbal products had been found to contain synthetic PDE-5 inhibitors, namely sildenafil, vardenafil, tadalafil, and their analogues. It is dangerous for public to consume these analogues due to unknown safety and toxicity profile. Hence, detection of such analogues is important.

OBJECTIVES: This study was to isolate, purify and identify acetildenafil analogue from herbal product.

METHOD: Thirty capsules from an adulterated herbal product, received by the NPCB from the Enforcement Division were chosen as sample. Six capsules were weighed and extracted with water and chloroform. The identification of the adulterant in the sample was analysed by TLC and IR. The extracted residues were purified by column chromatography packed with silica gel 60 using isocratic mobile phase. The isolated compound obtained was further identified by HPLC equipped with photodiode array detector using C8 column. Confirmation of the isolated compound is done by NMR. The study was carried out from July to October 2008.

RESULTS: Chromatographic and spectroscopic methods used showed the similarities in the main structure and functional groups of the unknown compound in sample with that of acetildenafil standard. Proton (^{1}H) and carbon-13 (^{13}C) NMR spectrums were used to confirm the identity of the compound as nor-acetildenafil.

CONCLUSION: The methods used in this study demonstrated that it is possible to isolate, purify and identify the adulterants in herbal products and provide an avenue for obtaining working standards from adulterated samples as alternative reference materials.

Keyword: actildenafil analogue, herbal product, High performance liquid chromatography (HPLC), Nuclear Magnetic Resonance (NMR)

PRESS RELEASE: SALE OF UNREGISTERED PRODUCT 'AMBERINE CAPSULE'

The public is advised to avoid buying and using a traditional product, 'Amberine capsule' with registration number MAL06021239T which is traditionally used for general well being and body health. The product registration holder for 'Amberine capsule' is Sne Marketing Sdn. Bhd. and the manufacturer is Nature's Grace (M) Sdn. Bhd.

The product registration for 'Amberine capsule'has been cancelled by the Drug Control Authority (DCA) at its 228th meeting on 27th May 2010 following the detection of scheduled poisons metformin and sibutramine. Metformin and sibutramine are not allowed to be formulated in a product which is classified as a traditional product.

Metformin and sibutramine can only be supplied by doctors or puchased at pharmacies with a prescription. The usage of metformin and sibutramine without proper diagnosis and monitoring by the doctor can cause serious adverse events. Metformin may reduce blood glucose (hypoglycaemic) and decrease renal function while sibutramine can cause an increase in blood pressure and other cardiovascular effects. Hence, these products can cause detrimental effects to consumers who are at high risk of getting these adverse events.

Since this product is confirmed to be adulterated with metformin and sibutramine, the public is advised to stop using it and seek for further advice from healthcare professionals if needed.
18 June 2010

CLASSIFICATION OF PRODUCTS THAT ARE APPLIED EXTERNALLY AROUND THE EYES AND PROHIBITED PACKAGING FOR THOSE PRODUCTS

Under the Quality Monitoring Program of notified cosmetic products in the market, the Cosmetic Section of Centre for Post Registration of Products, National Pharmaceutical Control Bureau (NPCB) has received reports and complaints regarding the sale of products such as the eye toner, which were originally notified as a cosmetic product for external application around the eyes as a moisturizer; have been misused as eye drops or sprayed into the eyes.

Those products that have been marketed with claims and advertisements such as for treatment to improve eyesight, to reduce short sightedness and to refresh the eye nerves which is obviously against the Medicines (Advertisement and Sales) Act 1956, ASEAN Cosmetic Directives and Guidelines for Control of Cosmetic Products in Malaysia.

Since those products are widely sold in the market, the NPCB has decided that cosmetic products that are used externally around the eyes are not allowed to be packed in containers similar to eye drops or eye spray bottles. This is to prevent those products from being misused as eye drops or eye sprays.

Products intended to be used as eye drops or eye sprays do not fall into the definition of cosmetic products. Those products are supposed to be regulated as pharmaceutical products which need to be manufactured in premises with Good Manufacturing Practice (GMP) certification. Premises that manufacture eye drop products must be specifically equipped for the production of sterile products.

Product holders who have notified those products as cosmetic products previously, are requested to recall the notified products involved immediately. Failure to do so will result in the cancellation of notification of those products as those products are no longer classified as cosmetic products due to the indication and the safety of those products are doubtful.

Selvaraja Seerangam
Director of Regulatory Pharmacy
National Pharmaceutical Control Bureau
Ministry of Health Malaysia
29 June 2010

PRESS RELEASE: THE SAFETY OF FISH OIL PRODUCTS

Products containing fish oil have been widely used as dietary supplement for many years. These products contain omega 3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In Malaysia, 196 products containing fish oil have been registered as dietary supplement. Products in pharmaceutical dosage forms (such as capsule and emulsion) have been formulated with other excipients to stabilize the product. Products containing fish oil that are registered by the Drug Control Authority (DCA) have been evaluated for their safety and quality, and are manufactured according to Good Manufacturing Practice (GMP). These products also need to undergo 'dioxin test' to ensure the dioxin level as they may be polluted with environmental pollutants.

The Ministry of Health has a monitoring programme to ensure the safety and quality of registered products available in the market. From year 2002 to 2010, there are only 4 adverse reports such as diarrhea, bloating, lethargy and lost of appetite received by the National Pharmaceutical Control Bureau (NPCB) concerning products containing fish oil.

There have been articles in the internet claiming fish oil can corrode polystyrene. However, the reports are very technical and cannot be implied to be directly related to causing harm due to the consumption of fish oil. In the mean time, the NPCB will monitor these products to ensure safety and acquire relevant information through regulatory network.

Consumers are encouraged to contact the NPCB when there is any doubt regarding fish oil products or if they encounter any side effects or adverse effects with these products by filling the adverse drug reactions (ADR) forms available from the NPCB website, www.bpfk.gov.my.

Eisah binti A. Rahman
Senior Director of Pharmaceutical Services
Ministry of Health Malaysia
7 April 2010

PRESS RELEASE: JINGZHI KESHOU TANCHUAN PILL REGISTERED IN MALAYSIA IS SAFE FOR CONSUMPTION

The National Pharmaceutical Control Bureau (NPCB) have received reports that a warning was issued by the Medicines & Healthcare Products Regulatory Agency of United Kingdom regarding "Jingzhi Keshou Tanchuan Pill" from China which was found to contain Aristolochic acid, of which the consumption may result in cancer. The above medication was re-packed in white plastic bottles and sold in the United Kingdom.

On 13th May 2010, The Senior Director of Pharmaceutical Services, Ministry of Health Malaysia, Madam Eisah bt. Abdul Rahman has stated that the result of analytical test conducted by the Drug Control Authority (DCA) showed that "Jingzhi Keshou Tanchuan Pill" sold locally does not contain Aristolochic Acid.

At present, there are only two registered products in Malaysia which contain Aristolochic Acid and five registered products containing Aristolochia species. To date, the ministry has not received any complaints on adverse effects related to the consumption of these products.

Aristolochic acid, when consumed, may result in the regression of the kidney function as well as cancer especially cancer of the urinary tract.

Eisah binti A. Rahman
Senior Director of Pharmaceutical Services
Ministry of Health Malaysia
13 May 2010

ALLOWABLE CONTENT OF LOVASTATIN IN NATURAL SOURCES FOR TRADITIONAL PRODUCTS

At the 227th Drug Control Authority (DCA) meeting, the committee has decided that the content of lovastatin in natural sources such as Red Yeast Rice (*Monascus purpureus*) for traditional products should be regulated and conform to agreed limits.

The dosage of traditional products containing Red Yeast Rice (*Monascus purpureus*) will be limited to an allowable content of lovastatin ≤ 10mg/ daily. Product registration holders are required to test the content of lovastatin in Red Yeast Rice (*Monascus purpureus*) in raw materials and also in finished products. The Certificate of Analysis (COA) for both raw materials and finished products are to be presented when application for registration is made. The content of lovastatin in the finished product has to be ≤ 1% w/w. Product registration holders are also required to ensure the daily intake of lovastatin does not exceed 10mg.

It is the responsibility of the product registration holder to ensure the content of lovastatin in each batch of raw materials and finished products sold in the market have been tested. Raw materials and finished products of Red Yeast Rice (*Monascus purpureus*) has to contain lovastatin ≤ 1% w/w. COA

for both raw materials and finished products has to be kept properly and the product registration holder will be required to present it to the authorities during surveillance programme.

A compulsory warning statement is required to be inserted into labels/package inserts of products containing Red Yeast Rice as below:

"This product contains naturally occurring lovastatin. Please consult your doctor/pharmacist before using this product."

"Do not take this product if you are already on statin products (lovastatin, atorvastatin, fluvastatin, pravastatin, simvastatin, rosuvastatin etc)."

"If you experience any allergic reactions or side effects such as lethargy, body and muscle aches, please stop using this product."

"Concurrent use of fibrates may cause sever myositis and myoglobinuria."

This requirement is effective from 3rd June 2010 onwards and it encompasses all new product registration applications and also those product registrations in the evaluation process. Nevertheless, for registered products, the product registration holder is allowed to use existing labels/package inserts until stocks are finished. A period of one year is given to make variation applications for the above matter to Variation Section, Centre for Post Registration of Products, National Pharmaceutical Control Bureau.

PRESS RELEASE: SALE OF UNREGISTERED PRODUCT '357 NASAL SPRAY'

The public is advised to avoid buying and using a traditional product, '357 Nasal Spray' with registration number MAL06061468T registered for use to relief nasal congestion. The product registration holder for '357 Nasal Spray' is Three Five Seven Sdn. Bhd. and the manufacturer is Qiandongnan Likaqing Tec Co. Ltd., China.

The product registration for '357 Nasal Spray' has been cancelled by the Drug Control Authority (DCA) at its 227th meeting on 29th April 2010 following the detection of scheduled poison, dexamethasone. Dexamethasone is not allowed to be formulated in a product which is classified as a traditional product.

Dexamethasone can only be supplied by doctors or purchased at pharmacies with a prescription. The usage of dexamethasone without proper diagnosis and monitoring by the doctor can cause serious adverse events such

as high blood pressure, edema and Cushingoid syndrome (moon face). Hence, this product can cause detrimental effects to consumers who are at high risk of getting these adverse products.

Since this product is confirmed to be adulterated with dexamethasone, the public is advised to stop using it and they seek for further advice from healthcare professionals if needed.

Eisah binti A. Rahman
Senior Director of Pharmaceutical Services
Ministry of Health Malaysia
19 May 2010

PRESS RELEASE: SUSPECTED COUNTERFEIT TRADITIONAL PRODUCT 'PO CHAI PILLS' ADULTERATED WITH DICLOFENAC

Department of Health, Hong Kong has cautioned the public through its press release on 22nd June 2010 regarding suspected counterfeit traditional product, 'Po Chai Pills' (batch number 21214) which is adulterated with diclofenac. This product is found to be different in external packing and the pills appeared to be darker in colour compared to the original product.

In Malaysia, the Drug Control Authority (DCA) has registered a single product manufactured by Li Chung Sing Tong, Hong Kong with the name of 'Poh Chai Pill' (registration number MAL19988034T) which is used traditionally for symptomatic relief of fever, cold, minor diarrhoea, vomiting and stomachache. The registration holder and also sole distributor of 'Poh Chai Pill' in Malaysia, Po Chai Herbal Technology (M) Sdn. Bhd. has confirmed that the adulterated product with batch number 21214 is not manufactured by Li Chung Shing Tong, Hong Kong.

Diclofenac is a pain killer that can cause side effects such as gastro-intestinal disturbances including gastric pain, nausea, vomiting, peptic ulcer and bleeding. Diclofenac is classified as a First Schedule drug under Poison Act 1952 and can only be supplied by doctors or pharmacists.

The general public is advised to be cautious when purchasing this product. Registered traditional products in Malaysia are evaluated to ensure quality and safety and it is mandatory for these products to carry the hologram sticker. The public, if in doubt, can verify the authenticity of such products at their nearest private community pharmacy.

Tan Sri Dato' Seri Dr Hj Mohd Ismail Merican
Director General of Health Malaysia
As DCA Chairman
Ministry of Health Malaysia
25 June 2010

DESCRIPTION OF SIBUTRAMINE CARDIOVASCULAR OUTCOME STUDY TO BE INCLUDED IN PACKAGE INSERTS OF SIBUTRAMINE PRODUCTS

The Drug Control Authority (DCA) at their 224th meeting held on the 28th January 2010 has decided that Sibutramine Cardiovascular Outcome (SCOUT) description study information is compulsory to be included in the package inserts of Sibutramine products. This is based on the result of SCOUT study for Reductil© products that has been carried out to evaluate the long term safety in obese and high risk of cardiovascular patients.

Descriptions of the study information that needs to be included in the package inserts of Sibutramine products are as below:

- The Sibutramine Cardiovascular OUTcomes (SCOUT) Study
- The SCOUT Study was a randomized, double-blind, placebo-controlled study, with a single-blind, sibutramine lead in period. The study was conducted as a post approval commitment to the European regulatory authorities.
- The study enrolled 10,744 and randomized 9,805 overweight or obese patients at high risk of cardiovascular events (the majority who were not indicated to receive treatment with the Sibutramine). In the study, these cardiovascular high risk subjects were treated with Sibutramine for up to 6 years and were not discontinued from treatment for inadequate weight loss response which is not consistent with the instruction for use.
- Subject treated with Sibutramine experienced 16% increased risk of a primary outcome event nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, or cardiovascular (CV) death (561/4906, 11.4%) compared to placebo treated subjects (490/4898, 10.0%) (hazard ratio 1.161 [95% CI 1.029, 1.31]; p=0.016) There was however no difference in the incidence of CV death or all cause mortality between the treatment groups.

Product Holders are also directed to produce the "Dear Healthcare Professional" letter to all medical practitioners who are related to the usage of the medicine. This decision covers all new registration applications as well as products which are still under evaluation.

However, for the registered products, the product holder is allowed to use the old package insert until all stocks are finished or if amendments need to be made in the package insert (amendments are applied through Variation Section, Centre for Post Registration of Products, National Pharmaceutical Control Bureau), the product holder is directed to fulfill the said requirement in the package inserts of Sibutramine products.

RE-EVALUATION OF REGISTRATION OF PRODUCTS CONTAINING A COMBINATION OF PARACETAMOL/ACETAMINOPHEN AND CAFFEINE IN MALAYSIA

The 227th Drug Control Authority (DCA) Meeting held on the 29th April 2010 has agreed to:

a. Allow the registration of products containing a combination of paracetamol/acetaminophen (non-poison) and caffeine to be under Control of Drug and Cosmetic Regulations 1984.

b. Allow the registration of products containing a combination of paracetamol/acetaminophen (non-poison) and caffeine to be exempted from Poison Act 1952.

c. Allow amendments to be made in Appendix 6 : List of prohibited ingredients (active) not allowed to be registered by the Drug Control Authority as below:

15. CAFFEINE – (EXCEPT for an oral preparation in combination with paracetamol/ acetaminophen)

d. Products containing a combination of paracetamol and caffeine for adult dose are allowed.

e. Products containing caffeine for pediatric are not allowed.

f. For products containing a combination of paracetamol and caffeine, dose unit of caffeine for adults is 65mg and maximum dose of caffeine is 520mg per day, meanwhile dose unit for paracetamol/acetaminophen is 500mg with the maximum dose of 4000mg per day and 8 tablets daily.

g. Additional warning in the label or package inserts for registered product containing a combination of paracetamol and caffeine is as below:

Special warning and precautions for products containing caffeine in combination with paracetamol;

- *Avoid other caffeine containing products. Too much caffeine may cause rapid heart rate, nervousness or sleeplessness.*
- *Ask a doctor or pharmacist before use if you have high blood pressure, glaucoma, or overactive bladder syndrome.*
- ***Do not exceed 8 tablets in 24 hours.***

- ***DO NOT*** *takes more than the recommended dose unless advised by your doctor. Use the smallest effective dose. Taking more than the maximum daily dose may* ***cause severe or possibly fatal liver damage.***
- ***DO NOT USE*** *with other drugs containing* ***paracetamol.***
- ***Not recommended for children under 12 years.***

h. Allowable packing size should not exceed 20 tablets/capsules.

i. Product containing a combination of caffeine, paracetamol/acetaminophen and aspirin is not allowed because:

a. Paracetamol/acetaminophen and Aspirin has similar mechanism of action which is similar anti-inflammatory activity (inhibition of prostaglandin synthesis).

b. In Appendix 6, Drug Registration Guidance Document states that products containing a combination of two or more analgesics with the same mode of action are not allowed to be registered.

c. In terms of safety, a combination of these two ingredients will cause worse adverse effects as compared to single use.

PROPOSAL TO INCLUDE "BOXED WARNING" IN PACKAGE INSERTS OF PROPYLTHIOURACIL PRODUCTS

The 228th Drug Control Authority (DCA) Meeting held on the 27th May 2010 has agreed for:

a. Amendments to be included in package inserts of propylthiouracil products under:

BOXED WARNING

Severe liver injury and acute liver failure, in some cases fatal, have been reported in patients treated with propylthiouracil. These reports of hepatic reactions include cases requiring liver transplantation in adult and pediatric patients.

Propylthiouracil should be reserved for patients who cannot tolerate methimazole/carbimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for the management of hyperthyroidism.

PROPOSAL TO INCLUDE THE WARNING STATEMENT OF "CONTRAINDICATED IN CHILDREN UNDER 2 YEARS OF AGE" IN PACKAGE INSERTS OF ALL CARBOCYSTEINE, ACETYLCARBOCYSTEINE AND METHYLCARBOCYSTEINE (MECYSTEINE) PRODUCTS

The 228th Drug Control Authority (DCA) Meeting held on the 27th May 2010 has agreed for:

a. Amendments to be included in package inserts of carbocysteine, metylcarbocysteine (mecysteine) and acetylcarbocysteine products under:

CONTRAINDICATIONS

Contraindicated in children below 2 years of age.

CONTACTS & MAP

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CENTRES	EXTENSION NO.
Centre for Product Registration	**5487**
• New Drug Section	5522
• Generic Medicine Section	5490
• Biotechnology Section	8423
• Complementary Medicine Section	8415
• Active Pharmaceutical Ingredient Section	8424
• Veterinary Medicine Section	5500
• Regulatory Coordination Section	5502
Centre for Post Registration	**5538**
• Surveillance and Product Complaints Section	5552
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• Variations Section	5588
• Cosmetic Section	5532
Centre for Organisational Development	**5553**
• Information Communication Technology Section	5555
• Quality System Section	5556
Centre for Compliance and Licensing	**5564**
• GMP Section	5566
• Quality, Certification, Licensing and GDP Section	5569
• Clinical Research and Compliance Section	5581
Centre for Quality Control	**5429**
• Bio-Pharmaceutical Testing Section	8457
• Research and Development Section	8448
• Pharmaceutical Chemistry Testing Section	5462, 5456, 5450
• Laboratory Services Unit	5431
• Natural Product Testing Section	5471
• Reference Standard Unit	5468
Centre for Administration	**8458**

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