

# HONG KONG PHARMACEUTICAL *JOURNAL*

VOL 22 NO 2 Apr - Jun 2015 ISSN 1727-2874



## News & Short Communications

**Developing Community Pharmacy in Hong Kong:  
A Focus on Lifelong Learning**

**An Interview of Mr. Mervyn David Loie, a former  
Chief Pharmacist at the Department of Medical  
and Health Services, Hong Kong**

**General Overview of Novel Oral Anti-Coagulants  
(2 CE Units)**

**A Brief Review on Clinical Data of Nutraceuticals  
Claiming to Treat Erectile Dysfunction**

**Study Visit to Beijing and the Forbidden City  
International Pharmacist Forum 2015**

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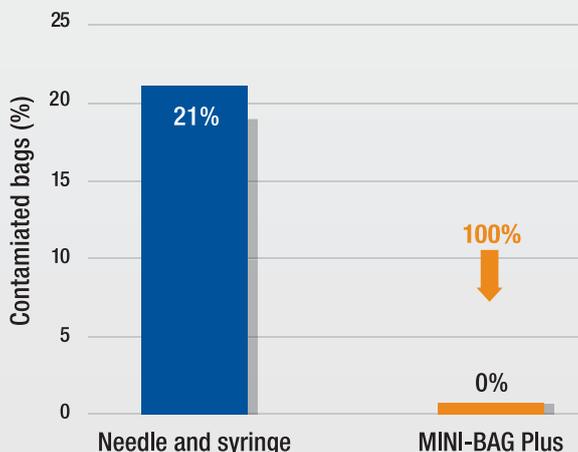
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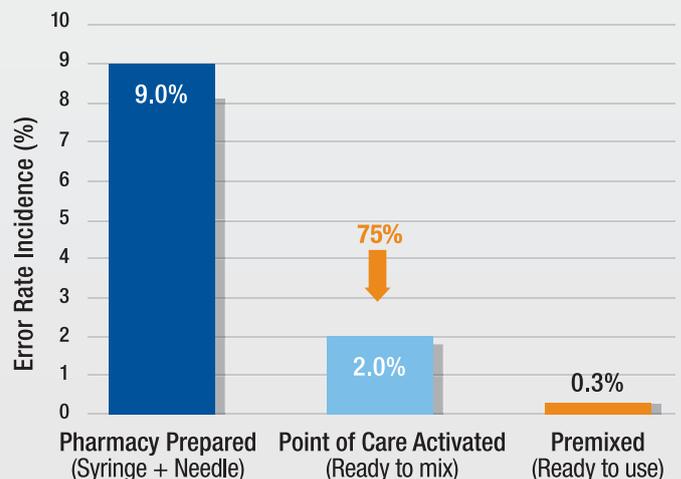
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<sup>1</sup> Nichols S, et al. Evaluation of the Baxter MINI-BAG Plus for ward preparation of cefuroxime / metronidazole infusion mixtures. Hospital Pharmacy. 2003; 10: 127-30

<sup>2</sup> Flynn EA, Pearson RE, Barker KN. Observational study of accuracy in compounding i.v. admixtures at five hospitals. American Journal of Health-System Pharmacy. 1997; 54: 904-12

<sup>3</sup> Ortega A, et al. Economic evaluation of Viaflex with vial adapter in a unit-dose distribution system. Pharmacy World & Science. 1999 Dec; 21(6): 278-80.

\* On ward comparison of reconstitution methods in a British Hospital

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The Hong Kong Pharmaceutical Journal is a journal of the pharmacists, for the pharmacists and by the pharmacists. Submissions are welcome for the following sections:

- Pharmacy Education & Practice
- OTC & Health
- Medication Safety
- Society Activities
- Drugs & Therapeutics
- Pharmaceutical Techniques & Technology
- Herbal Medicines & Nutraceuticals
- New Products

Comments on any aspects of the profession are also welcome as Letter to the Editor.

There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.

It is preferable to have original articles submitted as an electronic file, in Microsoft Word, typed in Arial 9pt. Files can be sent to the following address:

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For detail instructions for authors, please refer to the first issue of each volume of HKPJ.

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# Need for Ensuring Competence of Pharmacists by Life Long Learning



**Pharmacists** are trusted healthcare professionals in their local communities and pharmacy teams are increasingly taking on an expanded role in promoting health and wellbeing to those using their pharmacy's services. Community pharmacies are local businesses connected to their local communities and provide an ideal setting for the provision of public health services

because they are easily accessible with long opening hours and free consultations. In Hong Kong, there is currently over 2600 registered pharmacists and every year, around 60 pharmacy students will graduate from the Chinese University of Hong Kong and 30 will graduate from the Hong Kong University. Including graduates from overseas pharmacy schools, the number of registered pharmacists has increased at a rate of almost 100 per year. The role of pharmacists has changed from dispensing of drugs to the counselling of patients, medication review and public health education. With the increase knowledge of diseases and new drug discoveries, there is a need for pharmacists to keep up with the advances in medicine and drug knowledge by taking Continuing Education (CE) or Continuing Professional Development (CPD).

In the article written by Wynne Hui, Phoebe Chan and Eliza Tam (page 53), a literature research was done to overview the role of community pharmacist, as well as the framework and outcome of lifelong learning system in different countries (including England, United State of America, Australia, Singapore and Japan) and to compare the international trend with Hong Kong's current situation. Most of these countries, except Japan, require pharmacists to undertake CE or CPD for renewal of their pharmacists licenses. CE requires pharmacists to collect credit points by participating in lectures, workshops or literatures. CPD is defined by framework composed of reflection, planning, action, documentation and evaluating. Reflection means personal assessment of individual learning needs. Planning stands for the identification of actions required to meet their learning targets. Action is the participation of activities, for example workshops, self-study and tutoring. Documentation means recording details of the activities in portfolios. Evaluation is the estimation of personal benefits from the activities. Based on the cases reviewed, global trend shows the tendency and worthiness for a mandatory pharmacist lifelong learning system.

In Hong Kong, the Hospital Authority requires pharmacists to acquire some CE units annually but at present there is no mandatory requirement by the Pharmacy & Poisons Board for CE or CPD for the renewal of the annual pharmacist license. Pharmacist representatives from the 3 professional organizations and the 2 universities have formed the Pharmacy Central Continuing Education Committee to provide CE to the pharmacists 4 to 5 times a year. However, the organization was lacking in statutory status for recognition by the Primary Care Office. Despite our pledge that the pharmacists working in these pharmacies could show CE credits issued by the PCCC, the Office refused to list out the names of the pharmacies in their website. Last year, during the consultation of the Pharmacy and Poisons Amendment Bill 2014, various professional societies such as the PSHK, SHP, School of Pharmacy of CUHK and the Pharmacology and Pharmacy Department of HKU have voiced out the need of the establishment of the Pharmacy Council with the vision to be an independent statutory body that advocates superior professional standards in the management of drug product selection and patient

engagement. Its mission is to establish quality standards as a mechanism for advancing pharmacy practice with an overarching goal of providing safe and effective drug products to the public at an affordable price; to issue codes of practice of pharmacists and supportive personnel; to look into registration of pharmacists and continuing education requirements of pharmacists and to take disciplinary action against misconduct by pharmacists. The establishment of the Pharmacy Council would require law amendment. Some concerns were raised by community pharmacists that it will lead to higher licence fee, mandatory CEs and the cost of acquiring the CE units. We hope to gain partial subsidize of the fees by the government and eventually gain the support of the community pharmacists.

Mary Cheng and Patrick Chiu wrote about the interview with Mr. Mervyn Loie (Page 59) who joined the civil service as a student dispenser in 1948 and retired as a chief pharmacist of the Department of Medical and Health Services in 1984 after 36 years of service. Mervyn Loie has dedicated his life to public service in Hong Kong. In the 1960's, he worked in the pharmacy department of Kowloon Hospital and Queen Elizabeth Hospital and was responsible for the manufacturing and supply of the drugs to the government clinics and hospitals in the 70's. With his drug knowledge and dedication, he has taught and trained many dispensers for the government hospitals and clinics. Through his story, we have a better understanding of the development of the pharmacy service in Hong Kong from the 1950's to 1980's.

Chara Yip wrote a review article about the new oral anti-coagulants on page 64. In order to select the most appropriate new oral anticoagulants for different clinical scenario, it is essential to understand the differences, including the pharmaceutical properties and clinical evidences, between the new oral anti-coagulants. This article aims to provide an overview of the three emerging popular new oral anti-coagulants (dabigatran, rivaroxaban and apixaban), pharmacodynamics and pharmacokinetics, and the efficacy and safety data of these 3 new oral anti-coagulants are compared.

Erectile Dysfunction (ED) has been a common health issue worldwide, particularly in Asia. According to a population-representative survey, 36.7% of men aged 26 to 70 years suffered from ED in Hong Kong. Based on the results of a global survey, 89% and 85% of people with sexual dysfunction did not seek help from their physicians in China and Hong Kong, respectively. Nowadays, many patients with ED prefer to seek help from the internet rather than healthcare professionals. As there is a vast amount of information about complementary and alternative medicine (CAM) available on the internet, it is not surprising that a significant proportion of ED patients opt for nutraceuticals and/or traditional Chinese medicine as their initial treatment. LAO Cheng-Kin, Pedro Fong and Henry Tong wrote (on page 68) a brief review on clinical data of nutraceuticals claiming to treat ED.

The Pharmaceutical Society of Hong Kong has led a group of pharmacists and pharmacy students to Beijing to attend the Forbidden City Forum in May 2015 as well as to take the opportunity to visit the Peking Union Medical College Hospital as well as the Beijing United Family Hospital. The study visit is published on page 76.

I hope all of you will enjoy reading the journal at your leisure and have a nice summer!

*Mary Catherine Cheng*  
Managing Editor  
30<sup>th</sup> July 2015

Prepared by Kwan Him Shek, Leung Ho Cheung Brian, Tse Wai Tak Marco, Wong Chi Lap Raymond, Wong Lai Yan Janet

## Time for Reconsidering Paracetamol Use in Spinal Pain and Osteoarthritis

Date: April 1, 2015

Paracetamol is a first-line agent for treatment of spinal pain and osteoarthritis, according to current clinical guidelines. A systematic review and meta-analysis found weak and inconsistent evidence supporting use of paracetamol.

The efficacy and safety of paracetamol for lower back pain and osteoarthritis of the hip or knee were evaluated in the study. Totally 13 randomised and placebo controlled studies were included. 3 trials examined the use of paracetamol for lower back pain.. Paracetamol use did not improve disability or quality of life compared with a placebo use. 10 trials assessed the paracetamol use in osteoarthritis of the hip or knee. Clinically unimportant benefits, in terms of reduction of pain and disability, were found

when comparing use of paracetamol with a placebo. An increased likelihood of abnormal liver function test results compared with a placebo was observed. The authors however suggest the clinical relevance is uncertain.

The follow-up periods in the trials were not longer than 6 months. The long term effects of paracetamol use need further research. Apart from drugs, non-pharmacological treatments such as exercise have shown benefits in spinal pain and osteoarthritis management.

Source: [www.bmj.com](http://www.bmj.com)

## US *Pseudomonas aeruginosa* septicemia in Hospitalized Adults from 1996 to 2010: Shifting or Standing?

Date: May 1, 2015

*Pseudomonas aeruginosa* septicemia (PAS) has been associated with high mortality rates and substantial resource utilization. Nonetheless, the burden of PAS in the United States in recent years remains unknown.

This article referred to a retrospective analysis of the U.S. National Hospital Discharge Surveys between 1996 and 2010. Adult patients with an ICD-9-CM code for PAS (038.43) were included. The following parameters were reported, namely, incidence, in-hospital mortality, and hospital length of stay (LOS) for PAS discharges. Incidence was calculated as PAS discharges per 10,000 total adult discharges.

On the whole, 213,553 patients had a PAS discharge diagnosis throughout the study period. These patients had a median

(interquartile range [IQR]) age of 69 (55-78) years and were predominately men (61%) and white (75%). PAS incidence declined from 6.5 per 10,000 in 1996 to 3.1 per 10,000 in 2001, followed by an increase to 6.5 per 10,000 in 2010. PAS incidence was the highest in the Northeast (7.6 per 10,000) and lowest in the South (6.2 per 10,000). The overall mortality rate was 16%, but this ranged from 10% to 26% over the study period. Median LOS was 10 (IQR, 6-19) days, and this varied over the study period (8-13 days).

It was concluded that the incidence of PAS had been increasing among hospitalized adults in the United States since 2001, with little evidence of improvement in mortality or LOS.

Source: [www.ajicjournal.org](http://www.ajicjournal.org)

## Arrhythmia Patients Taking Digoxin has Higher Risks of Death

Date: May 6, 2015

The largest meta-analysis to review digoxin has concluded that the treatment is associated with increased mortality in atrial fibrillation or heart failure patients. The researchers warned that digoxin should be used cautiously with patients' plasma levels being monitored carefully.

This meta-analysis was published in the European Heart Journal including 19 studies with 326426 patients being studied. Among patients receiving digoxin treatment, 21% higher risk of death was shown from any cause comparing to patients not receiving digoxin treatment (29% increase for atrial fibrillation and 14% increase for congestive heart failure patients).

Digoxin has been used for over 200 years and recommended by international guidelines, but it is still difficult to be used safely because

of its narrow therapeutic window. Regular blood tests are needed to measure the levels of digoxin in the blood.

The study leader and professor of cardiology at the The Goethe University Frankfurt, Stefan Hohnloser said he felt that the time of digoxin was over particularly in the use of controlling heart rate in atrial fibrillation, although digoxin has been used for decades and 1/3 of atrial fibrillation cases.

In conclusion, Digoxin, particularly at high levels, affects the heart's rhythm and pumping ability which may be involved in death-relating mechanisms. The situation can even get worse when interacting with other drugs.

Source: [www.bmj.com](http://www.bmj.com)

## Ticagrelor Shows Significant Cardiovascular Benefits Except Major Bleeding

Date: May 7, 2015

Ticagrelor, a P2Y<sub>12</sub> receptor antagonist with established efficacy after an acute coronary syndrome, was investigated in terms of its efficacy and safety in a study.

21,162 patients who had had a myocardial infarction 1 to 3 years earlier was randomly assigned to ticagrelor at a dose of 90 mg twice daily, ticagrelor at a dose of 60 mg twice daily, or placebo. All the patients were to be treated with aspirin in low-dose and were followed for a median of 33 months.

The two ticagrelor doses each reduced, as compared with placebo, the rate of cardiovascular death, myocardial infarction, or stroke, with Kaplan–Meier rates at 3 years of 7.85%, 7.77% and

9.04% respectively in 90 mg ticagrelor twice daily, 60 mg ticagrelor twice daily and placebo groups.

Rates of Thrombolysis in Myocardial Infarction major bleeding were higher with ticagrelor than with placebo, with the rates of intracranial hemorrhage or fatal bleeding in the three groups being 0.63%, 0.71%, and 0.60%, respectively.

In conclusion, treatment with ticagrelor significantly reduced the risk of cardiovascular death or stroke in patients with myocardial infarction but increased the risk of major bleeding.

Source: [www.nejm.org](http://www.nejm.org)

## SGLT2 Inhibitors May Cause Acidosis

Date: May 15, 2015

The U.S. Food and Drug Administration (FDA) has raised an alert for ketoacidosis caused by use of sodium-glucose cotransporter-2 (SGLT2) inhibitors, including canagliflozin (Invokana), dapagliflozin (Farxiga), and empagliflozin (Jardiance). The issue and the need for changes in the prescribing information are now under continuing investigation.

SGLT2 inhibitors are FDA-approved for use in adults with type 2 diabetes, for lowering the blood glucose level with diet and exercise. Cases of diabetic ketoacidosis, ketoacidosis or ketosis in patients treated with SGLT2 inhibitors were identified in the FDA Adverse Event Reporting System (FAERS) database. From March 2013 to June 6, 2014, 20 cases of related acidosis were reported

and additional FAERS reports have been received since June 2014. Major illness, reduced food and fluid intake, and reduced insulin dose were identified as triggering factors in some reports.

Patients should be aware of the possible symptoms including difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness, and seek medical help if they experience these symptoms. Discontinuation is necessary upon confirmation of acidosis. Health care professionals and patients are urged to report side effects associated to SGLT2 inhibitors use.

Source: [www.fda.gov](http://www.fda.gov)

## High-dose Ibuprofen: Cardiovascular Risk Similar to COX-2 Inhibitors

Date: May 23, 2015

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) and is a pharmacy-only medicine in Hong Kong. EMA's Pharmacovigilance Risk Assessment Committee (PRAC) confirmed a small increased risk of cardiovascular problems, such as heart attacks and strokes, in patients taking high doses of ibuprofen (at or above 2,400 mg per day). The review clarifies that the risk with high-dose ibuprofen is similar to the risk seen with some other NSAIDs, including COX-2 inhibitors and diclofenac.

To minimize the cardiovascular risk, high doses of ibuprofen (2,400 mg per day or higher) should be avoided in patients with serious underlying heart or circulatory conditions, such as heart failure, heart disease and circulatory problems or in those who have

previously had a heart attack or stroke. No increase in cardiovascular risk is seen with ibuprofen at doses of up to 1,200 mg per day.

The review also looked at data on the interaction between ibuprofen and low-dose aspirin when the latter is taken to reduce the risk of heart attacks and strokes. Laboratory studies have shown that ibuprofen reduces the blood-thinning effects of aspirin. However, it remains uncertain whether long-term use of ibuprofen in clinical practice reduces the benefits of low-dose aspirin in preventing heart attacks and strokes. Occasional use of ibuprofen should not affect the benefits of low-dose aspirin.

Source: [www.drugoffice.gov.hk](http://www.drugoffice.gov.hk)

## Chlorhexidine Daily Bathing: Effective Against Health-care Associated Infections Caused by Gram-negative Bacteria?

Date: June 1, 2015

Health care-associated infections (HAIs) have been much associated with morbidity and mortality in intensive care unit (ICU) patients. Focusing on the causative bacteria, the study was designed to evaluate the impact of daily bathing with chlorhexidine gluconate (CHG) on the incidence rates of HAIs in a French ICU.

Between March 2012 and May 2013, there was an enrollment of in total 325 patients, with at least 1 episode of suspected sepsis in

the ICU, during two 6-month periods. On one hand, the intervention group was subjected to daily skin cleansing with 2% CHG-impregnated cloths; on the other hand, the control group was bathed daily with soap and water.

HAI ranged from bloodstream infections to ventilator-associated pneumonia and urinary tract infections, while incidence rates corresponded to the number of infections per 1,000 patient days.

A statistically significant drop in incidence of HAI was achieved in the intervention group (29 vs 56;  $P = .01$ ). After adjustment for baseline patient characteristics, the increased risk of HAI in the water and soap group was statistically significant (odds ratio = 1.993; 95% confidence interval [CI], 1.132-3.508;  $P = .017$ ). The incidence rate of clinical cultures positive for gram-negative bacteria, including *Enterobacteriaceae* and non-fermenting bacilli, dropped

in the intervention group (risk ratio = 0.588; 95% CI, 0.346-0.978;  $P = .04$ ).

It was concluded that CHG daily cleansing reduced the incidence rate of HAI caused by gram-negative bacteria, whereby the role of transient gram-negative bacteria skin colonization in the pathogenesis of HAI was highlighted.

Source: [www.ajicjournal.org](http://www.ajicjournal.org)

## What If Insulin can be Inhaled?

Date: June 2, 2015

The FDA has approved an inhaled, rapid-acting, dry powder formulation of recombinant human insulin (Afrezza – Mannkind/Sanofi) for treatment of adults with type 1 or type 2 diabetes. In patients with type 1 diabetes, the drug must be used in combination with long-acting insulin.

In an unpublished pharmacokinetic studies comparing Afrezza and insulin lispro, it was shown that serum concentrations peaked earlier with Afrezza, but the onset of action was similar with both drugs. The maximum effect occurred about 50 minutes after administration of Afrezza and about 120 minutes after injection of insulin lispro. Inhaled insulin had a shorter duration of action than insulin lispro. Afrezza was also found of similar efficacy in lowering HbA1c to biaspart insulin.

However, Afrezza has notable adverse effects. 27% of patients experience throat pain or irritation and cough, as the main reason for discontinuation. A decrease in forced expiratory volume in one second (FEV<sub>1</sub>) by 40 mL was observed, which started within 3 months of treatment and persist for 2 years, contraindicating the drug in chronic lung disease such as asthma and chronic obstruction pulmonary disease (COPD).

Afrezza is not yet approved by the Pharmacy and Poisons Board. It appears to be only modestly effective in reducing HbA1c. Cough is a common side effect and the long-term pulmonary safety of inhaling insulin is unknown.

Source: [medicalletter.org](http://medicalletter.org)

## Antidepressant Use Late in Pregnancy and Risk of Persistent Pulmonary Hypertension of the Newborn

Date: June 2, 2015

Persistent pulmonary hypertension of the newborn is associated with substantial morbidity and mortality. The association between selective serotonin reuptake inhibitor (SSRI) antidepressant use during pregnancy and risk of persistent pulmonary hypertension of the newborn (PPHN) has been controversial. A cohort study was performed in to examine the risk of PPHN associated with exposure to different antidepressant medication classes late in pregnancy.

In 2000-2010, a total of 3,789,330 pregnant women with a diagnosis of depression were enrolled in the study. The exposure was either SSRI and non-SSRI monotherapy use during the 90 days

before delivery or no use. The main outcome was recorded diagnosis of PPHN during the first 30 days after delivery. It was found that SSRI exposure in late pregnancy may be associated with an increase in the risk of PPHN, but the magnitude of that risk is smaller than previous studies have suggested. Sensitivity analyses applying more stringent definitions of exposure (>1 dispensing) and outcome (PPHN with ventilatory assistance or extracorporeal membrane oxygenation) did not amplify the degree of observed risk. There was no evidence of a significantly increased risk associated with non-SSRI antidepressant medication use.

Source: [jama.jamanetwork.com](http://jama.jamanetwork.com)

## Anti-TNF Induced Infection is Site-specific, Study Finds

Date: June 5, 2015

Being an important pro-inflammatory mediator, tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitors are highly effective in the treatment of several immune mediated diseases, including inflammatory bowel diseases (IBD). The most commonly used TNF- $\alpha$  inhibitors in people with inflammatory bowel disease are infliximab and adalimumab for the treatment of Crohn's disease, whereas only infliximab and adalimumab are approved for the treatment of ulcerative colitis.

By cross referencing the Danish civil registration system and other national registries, the research team identified patients with Crohn's disease and ulcerative colitis, and ascertained history of comorbidities and histories of TNF- $\alpha$  inhibitor uses. They were studied whether, after the use of such drugs, serious infections occur in the divided subgroups including respiratory tract infections,

gastrointestinal infections, urological or gynaecological infections, skin and subcutaneous tissue infections, sepsis, and other infections (such as opportunistic infections and tuberculosis).

A cohort of 4300 people with IBD and TNF- $\alpha$  inhibitors prescribed was identified and the hazard ratios were calculated for each subgroups of serious infections. Sepsis, urological or gynaecological infections, skin and soft tissue infections were found to be of high risks. The results suggest that clinical vigilance of potential infectious complications is indicated in people treated with TNF- $\alpha$  inhibitors for inflammatory bowel disease, especially early in the course of treatment.

Source: [www.bmj.com](http://www.bmj.com)

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- ▶ Regression of fibrosis or cirrhosis<sup>6</sup>

**Abbreviated Prescribing Information (HK-SEP11-US-OCT10)**

**Presentation:** Film-coated tablet containing 300 mg of tenofovir disoproxil fumarate (TDF). **Indications:** 1. Treatment of chronic hepatitis B (CHB) in adults. 2. In combination with other antiretroviral medicinal products for treatment of HIV-1 infected adults and pediatric patients 12 years of age and older. **Dosage:** Adults: One tablet once daily taken orally, without regard to food. **Pediatric patients:** CHB: Not recommended; HIV-1: One tablet once daily taken orally, without regard to food for patients  $\geq 12$  years of age and  $\geq 35$  kg. **Elderly:** Insufficient data to make dose recommendations for patients  $>65$  years. The dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance  $<50$  mL/min. **Contraindications:** None. **Warnings and Precautions:** Lactic acidosis/severe hepatomegaly with steatosis; severe exacerbation of hepatitis after discontinuation of anti-HBV treatment; new onset or worsening renal impairment; coadministration with products containing TDF or adefovir dipivoxil; patients coinfecting with HIV-1 and HBV; decreases in bone mineral density; fat redistribution; immune reconstitution syndrome; early virologic failure. **Interactions & Side effects:** refer to Package Insert.

**Before prescribing, please consult full prescribing information which is available upon request.**

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 **GILEAD** Gilead Sciences Hong Kong Limited

Room 2603, 26th Floor, Hysan Place, 500 Hennessy Road, Causeway Bay, Hong Kong Tel: (852) 3129 2037 Fax: (852) 2856 2611

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## Developing Community Pharmacy in Hong Kong: A Focus on Lifelong Learning

HUI, Wynne CM\* ; CHAN, Phoebe WL ; TAM, Eliza YT

*Department of Pharmacology and Pharmacy, 2/F Laboratory Block, 21 Sassoon Road, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR*

*(\*Corresponding author. Email: cherryh0210@yahoo.com.hk)*

### ABSTRACT

Community pharmacy in Hong Kong plays a significant part in Primary Health Care by provision of pharmaceutical care service. The role of community pharmacist has been evolving from traditional dispensing to proactive patient counselling and clinical services. There is a need of lifelong learning to ensure their competence as health care professional. A literature research was done to overview the role of community pharmacist, as well as the framework and outcome of lifelong learning system in different countries (including England, United State of America, Australia, Singapore and Japan) and to compare the international trend with Hong Kong's current situation. The result of this review shows a global shift of community pharmacist's role towards patient counselling. Mandatory continuing education or continuing professional development has been widely adopted by reviewed countries, with several similarities identified: government-accredited learning activities, quantitative measurement of pharmacist's achievement and a comprehensive framework concept. Compared to other countries, Hong Kong is still at beginning stage of lifelong learning system development. Studies should be done to investigate pharmacists' interests and practical needs in Hong Kong, which can assist the development of learning programmes adaptable to local practice. Results from this review may serve as a basis for future direction of pharmacist lifelong learning system implementation in Hong Kong.

**Keywords:** *continued education, continued professional development, community pharmacist, primary health*

### INTRODUCTION

Primary Health Care has taken a fundamental role in health care system worldwide since the Alma Ata declaration in 1978. According to the World Health Organization (WHO), Primary Health Care was defined as "essential health care based on practical, scientifically sound and socially acceptable methods and technology, made universally available to individuals and families in the community through their full participation and at a cost that the community and country can afford to maintain at every stage of their development in the spirit of self-reliance and self-determination".<sup>(1)</sup> The definition underlines "community" as the main focus of Primary Health Care, and through which health for all would be achieved.

Pharmacotherapy is one of the most important types of treatment used in health care service.<sup>(2)</sup> Being a pharmacotherapy specialist, pharmacists should bear the responsibility and contribute to ensure the quality of Primary Health Care, by safeguarding the rational use of medicine. In the recent years, pharmacist's duty has been expanding from traditional dispensing to patient counselling and public health education.<sup>(3)</sup> With no appointment needed and easily reachable location, community pharmacy in Hong Kong can be more accessible than other settings. Therefore, community pharmacists are at the best position to contribute to Primary Health Care by the provision of pharmaceutical care.

The concept of pharmaceutical care was defined by the International Pharmaceutical Federation (FIP) as "The responsible provision of drug therapy for the purpose of achieving definite outcomes that improve or maintain a patient's quality of life".<sup>(2)</sup> In this definition, the key word is "patient". Community pharmacy should enhance a patient-centered service to meet patient's expectations and pharmaceutical needs. Registered and practising community pharmacists are equipped with professional knowledge and skills through pharmacy education provided by universities. However, with the fast evolution of new diseases and new medicines, as well as easy accessibility of medical information from internet, patient's expectations of community pharmacy service are predicted to expand in the foreseeable future. Therefore, pharmacists have to keep their medical knowledge up to date, so as to ensure their competence as pharmacotherapy specialist.<sup>(4)</sup> This idea complies with the concept of "seven-star pharmacist" introduced by WHO and FIP in the Good Pharmacy Education Practise, which described pharmacist as: caregiver, decision-maker, communicator, manager, teacher, leader and what is being discussed now, life-long learner.<sup>(2)</sup>

Internationally, governments and professional medical associations in different countries have already started implementing formal and compulsory lifelong learning systems, with the aim of motivating a healthcare practitioner to further pursue professional knowledge and to ensure the quality of health care service.<sup>(5)</sup> In 2002, FIP adopted the concept of Continuous Professional Development (CPD) and defined it as "the responsibility of individual pharmacists for systemic maintenance, development and broadening of knowledge, skills and attitudes, to ensure competence as a professional throughout their careers".<sup>(6)</sup> Despite the fact that some

countries are implementing this concept for their pharmacist lifelong learning system, some countries are still following the traditional Continuing Education (CE), and others, including Hong Kong, do not have any compulsory lifelong learning programme.<sup>(4)</sup>

According to Pharmacy and Poison's Board of Hong Kong, the number of Authorized Sellers of Poisons in Hong Kong is continuously increasing, revealing the growing demand of high-quality community pharmacy service.<sup>(7)</sup> Given the significance of lifelong learning in ensuring professionalism of pharmacist, the value of implementation of a mandatory lifelong learning system in Hong Kong is worth debating.

In this respect, this review aims to investigate and compare the role of community pharmacists, as well as the frameworks and outcomes of lifelong learning systems in different countries. Developed countries including England, United State of America and Australia were selected due to their role as global leaders of pharmacy profession development. Singapore and Japan, the neighboring countries of Hong Kong, in which the population is mainly composed of Asian, were also chosen. The result of review may provide ideas and guides for the future implementation of formal lifelong learning system in Hong Kong.

### **Global trend of pharmacist lifelong learning**

Countries where the pharmaceutical care services are internationally recognised at a more advanced level, have implemented mandatory lifelong learning system for pharmacist based on the concept of either Continuing Education (CE) or Continuing Professional Development (CPD). These countries include England, the United State of America, Australia and Singapore.

The definition of the type of system is based on the requirements to be met by pharmacists. CE requires pharmacists to collect credit points by participating in lifelong learning activities, which are usually in traditional education format, including lectures, workshops or literatures.<sup>(8)</sup> CPD is defined by a learning cycle or framework composed of reflection, planning, action, documentation and evaluating. Reflection means personal assessment of individual learning needs. Planning stands for the identification of actions required to meet their learning targets. Action is the participation of activities, for example workshops, self-study and tutoring. Documentation means recording details of the activities in portfolios. Evaluation is the estimation of personal benefits from the activities.<sup>(9)</sup>

The CPD process requires the participating pharmacists to plan their own targets, self-direct the learning progress and evaluate their performance and outcome. Pharmacists are required to record the details in a portfolio, which would be reviewed by responsible committee.

The major differences between CE and CPD framework is the development approach and direction. CE activities are structured to target general pharmacy profession development, which aims to broaden pharmacy knowledge base and improve patient counselling skill of the whole pharmacy profession. In

contrast, CPD activities are solely selected by the pharmacist himself. Individual training needs of pharmacists are resolved by self-directed and outcome-focused lifelong learning.<sup>(8)</sup>

In this article, few countries were selected as examples to illustrate the global trend of pharmacist role, the detailed framework of CE and CPD, as well as the outcomes.

### **England (UK)**

In 1948, the National Health Service (NHS) was developed in England, providing a framework for community pharmacy to deliver pharmaceutical services under the guidance of contract. Since then, community pharmacy is recognised as one of the major contributors to primary health care.<sup>(10)</sup> The introduction of Medicines Use Review and Prescription Intervention Service (MUR) in 2005, shifted the community pharmacists' role from unidirectional drug information education to patient-initiated counselling, giving them opportunity to better contribute in pharmaceutical care and public health education.<sup>(11)</sup>

Under the implementation of policies, community pharmacists in England have picked up the roles of monitoring and dispensing on prescription, counselling patients on prescribed and over-the-counter medicines, responding to symptoms and providing services to nursing homes.<sup>(12)</sup>

Compulsory lifelong learning system was developed to ensure quality of pharmaceutical care service. Replacing the previous mandatory Continuing Education (CE) framework, which required pharmacists to undertake 30 hours of CE each year, England became one of the earliest countries to adopt the Continuing Professional Development (CPD) concept.<sup>(5)</sup> In 1996, the potential for CPD to be introduced in England was first recognised. A pilot project was started in 1998 by the Royal Pharmaceutical Society of Great Britain and the framework was refined afterwards.<sup>(13)</sup> Began in 2010, the "Plan and Record" CPD framework was recommended by both the Royal Pharmaceutical Society and the General Pharmaceutical Council.<sup>(14)</sup>

Currently, all registered practising pharmacists in England are legally required to complete at least nine CPD records annually, in order to maintain their registration as pharmacists.<sup>(15)</sup> Pharmacists are required to enhance their competence by following the CPD cycle, through which they should "reflect" what they might need to improve, "plan" how they will achieve the target, take appropriate "action", and "evaluate" the beneficial outcome. There is no definite guideline on the CPD activity requirement. Pharmacists can choose any topics related to their profession and learn through any activities. Qualitative control is established by the Royal Pharmaceutical Society. CPD records would be regularly collected for review and detailed feedbacks would be given to ensure the quality of pharmacist self-directed learning.<sup>(16)</sup>

No current studies about the outcome of the CPD system in England are available. However, pharmacist's point of view towards CPD system can be considered, in order to investigate the acceptability of the newly adopted educational concept. According to a comprehensive review article summarising twenty-two studies, English pharmacists' attitude towards CPD

was identified. Pharmacy professionals in England generally support the principle of CPD. However, eight barriers were reported, including time, financial and resource, understanding of the principle, facilitation and support, motivation and interest, attitude towards compulsory nature, system constraints and technical problems.<sup>(17)</sup>

### **United State of America (USA)**

In USA, community pharmacies are composed of traditional chain pharmacies, mass merchandisers and supermarkets. In recent years, the primary focus of community pharmacists has evolved from traditional dispensing prescribed drugs to patient-based pharmaceutical care service, mainly in form of counselling.<sup>(18)</sup>

Boards of pharmacy in the 50 states, the District of Columbia, Gram, and Puerto Rico are responsible to regulate pharmacy profession in USA. Despite the differences in fundamental registration criteria, pharmacists are required by the boards to complete specific hours of board-approved CE annually to renew their licences.<sup>(19)</sup> An average of 15 hours CE per year is required. Some boards requested additional requirements for the format and topic involved. For example, certain hours of live courses or activities related to pharmacy law should be included. Instead of individual educational activities, only recognised CE activities provided by CE providers accredited by the Accreditation Council for Pharmacy Education (ACPE) are accepted.<sup>(20)</sup> The ACPE-accredited providers are responsible to plan the CE activities, which are based on the five pharmacist professional goals: providing patient-based care, playing a role in interdisciplinary team, dispensing in an evidence-based manner, improving service quality, and handling information technology.<sup>(21)</sup>

In recent years, evidences point out the need to modify the selection criteria of CE educational activities, for instance the consideration of pharmacist's interest or preference, as well as the applicability during daily practice.<sup>(20)</sup> Therefore, the CPD system has been in discussion in USA and is considered to be implemented to improve the existing CE system. A five-state CPD pilot programme was started in 2006, providing valuable strategies for possible future application of the CPD concept.<sup>(20)</sup>

### **Australia**

Community pharmacies have been taking a key position in government's National Medicines Policy in Australia, in which pharmacists are responsible to provide the public with cognitive pharmaceutical services (CPS), promote effective and safe drug usage based on their professional knowledge and experience.<sup>(22)</sup> To ensure the quality of CPS, community pharmacists in Australia are responsible for drug provision, counselling, clinical intervention and disease preventive care.<sup>(23)</sup>

Since 2009, pharmacists in Australia are legally required to obtain a minimal of 40 CPD credits each year for the renewal of registration. According to guidelines from the Pharmacy Board of Australia, CPD standard can be met by either joining the Australian Pharmacy Council accredited activities or performing non-accredited self-directed learning. There is no strict guideline on the details of CPD activities. Only three requirements were set up to give pharmacists a general direction on what to be

included in their individual learning activities: the activities must be relevant to pharmacist's duty, the content must be practical in their daily practice and the activities must be organised by qualified parties.<sup>(24)</sup> Pharmacists are expected to choose CPD activities that suit their individual needs in accordance to the National Competency Standards Framework for Pharmacists in Australia. A learning plan should be developed and regular self-review is needed.<sup>(25)</sup>

There is lack of objective study measuring the effectiveness of the CPD framework. However, based on a survey research, pharmacists in Australia generally agree that CPD system is a positive move to improve pharmaceutical service. The role of cognitive service provision appears to further motivate community pharmacists to maintain lifelong learning through the CPD model.<sup>(26)</sup>

### **Singapore**

The service provided by community pharmacies in Singapore ranges from giving advice for over-the-counter drugs to counselling on disease management. However, limited dispensing can be seen, which may due to the lack of separation between medication prescribing and dispensing.<sup>(27)</sup>

Despite of that, lifelong learning for pharmacist is compulsory in Singapore under the system of Continuing Professional Education (CPE), which definition is the same as CE, for the renewal of practising certificate. The system was legally implemented under the Pharmacists Registration Act in 2008 and operated in a 2-year cycle manner. A quantitative point awarding system is involved, in which each pharmacist should obtain at least 50 points in a 2-year cycle. CPE points can be obtained by attending 3 categories of activities provided by Singapore Pharmacy Board accredited CPE providers. The activities include participation in live events, publishing original papers and involving in formal- or self-study, all of which must be related to pharmacy profession. After completion of activities, pharmacists should update their CPE credit balance, which would be reviewed by Board.<sup>(28)</sup>

A survey interviewing 840 pharmacists conducted in 2011 revealed that pharmacists generally agreed with the significance of CPE in Singapore, especially when considering professionalism. About three quarters of interviewees believed that compulsory CPE can improve the standard of pharmacy profession, supported by statistics of more than half of the pharmacists regarded CPE as a system which enhances their medical knowledge (70%), encourages lifelong learning (64%) and helps self-evaluation (58%).<sup>(29)</sup>

### **Japan**

The healthcare system in Japan has continuously undergoing development to tackle the aging problem in recent years. Community pharmacy takes an important role in the reforming system, as dispensing on prescriptions and counselling are the major role of community pharmacists.<sup>(30)</sup>

To offer learning resources and opportunities for all pharmacists, the Japan Pharmacists Education Centre (JPEC) was established in 1989, developing the CE framework in Japan. Pharmacists may voluntarily join different

CE programmes, namely General Continuing Education Credentialing Programmes, Special Training Programmes and Pharmacy Specialties Credentialing Programmes. In 2004, Council on Pharmacists' Credentials was established, providing further convenience for pharmacists by acting as CE provider accreditor.<sup>(31)</sup>

After the proposal of CPD system by FIP, the Japan Pharmaceutical Association Lifelong Learning Support System (JPALC) was launched, allowing pharmacists to record their learning progress on a web-based portfolio system voluntarily.<sup>(8)</sup>

Up till 2013, around 10% of registered pharmacists (20,000 pharmacists) have applied to participate in the programme.<sup>(8)</sup> But currently, no evidence about the outcome of the programme can be approached due to barrier of language.

### Hong Kong

There are over 600 community pharmacies in Hong Kong, most of which are located within easy reach by the public. This feature makes community pharmacists to bear a major role in providing primary health care services, taking up the daily duties of dispensing, drug information education, basic health screening and disease management.<sup>(32)</sup>

Up till now, no mandatory lifelong learning system is available for registered pharmacists in Hong Kong. The Pharmacy Central Continuing Education Committee was collaboratively set up by six organizations: Department of Pharmacology and Pharmacy, the University of Hong Kong; Hong Kong Pharmacists (Public Service) Association; Pharmaceutical Society of Hong Kong; Practising Pharmacists Association of Hong Kong; The Chinese University of Hong Kong (School of Pharmacy) and Society of Hospital Pharmacists of Hong Kong. Except for the members of the six parties, pharmacists need to pay an annual fee to enroll for the CE programmes. CE units will be awarded by joining CE programmes or writing articles. Certificates will be issued to the pharmacist gaining a minimum of 20 CE units in a year.<sup>(33)</sup>

Educational workshops also occasionally take place for community pharmacists working in chain stores. It is noted, however, that workshop organisers are usually pharmaceutical companies, and the objectivity of the materials is worth considering.

### PHARMACIST PERCEPTIONS AND GENERAL OUTCOMES

Internationally, a number of survey-based researches have revealed pharmacists' attitudes and perceptions towards CE and CPD.<sup>(8)</sup>

In general, pharmacists are supportive towards the concept of CE and CPD. A study identified that under the CE system, pharmacists are encouraged to undergo lifelong learning due to three facilitators, including increased desire to enrich knowledge, mandatory requirement for practising license renewal and relaxation via the escape from routine job.<sup>(34)</sup> Other studies in USA and Scotland revealed that most of the pharmacists understand the definition of CPD and spend an average of 40 hours per year on CPD.<sup>(35,36)</sup>

However, factors discouraging pharmacists from participating CE and CPD have also been identified. A survey conducted in Egypt discovered the major obstacles against CE are lack of time, over-workload and extra cost.<sup>(37)</sup> Scottish pharmacists were interviewed and listed out four significant factors necessary to motivate CPD participation, including workplace support, easy access to resources, trust in CPD framework and personal desire to participate. Community pharmacists were found to require more motivating factors among all registered pharmacists, which implied they are the least willing to join the CPD programme.<sup>(38)</sup>

Despite pharmacists' viewpoint and extend of understanding towards the frameworks, general outcomes of CE and CPD systems were measured, but in a subjective way. A randomized, controlled study divided pharmacists into two groups and instructed them to participate in either CE or CPD programme. Questionnaires were given after 10 months to measure the outcome experienced by the pharmacists compared to baseline. After follow up, both groups reported better communication and cooperation with other health care professionals (CE participants: 6% ; CPD participants: 32%), improved patient care skills (CE participants: 23% ; CPD participants: 46%), enhanced medical knowledge (CE participants: 6% ; CPD participants: 34%) and better attitudes as a profession (CE participant: 11% ; CPD participants: 43%). From the study result, CPD participants tended to be more likely to report a positive change than CE participants during follow up period. However, CPD programme also discouraged pharmacists to a greater extend due to time-consuming characteristic.<sup>(39)</sup>

### DISCUSSION

The shift of role towards a more patient-centered care and the evolvement of duties undertaken by community pharmacists directly determine the need of lifelong learning programme. Globally, community pharmacists have proliferating responsibilities over primary health care. In UK, US, Australia

| Country                    | System         | Requirements                   | Activities criteria  | Outcome/Pharmacist's attitude                       |
|----------------------------|----------------|--------------------------------|--|---|
| UK <sup>13-17</sup>        | Compulsory CPD | Minimum 9 CPD records per year | Pharmacist's own choice, related to pharmacy profession                  | Generally support the concept, pointed out barriers |
| USA <sup>19-21</sup>       | Compulsory CE  | 15 hours CE per year           | Provided by accredited providers, based on pharmacist professional goals | Not available                                       |
| Australia <sup>24-26</sup> | Compulsory CPD | 40 CPD credits per year        | Accredited or non-accredited activities, based on individual need        | Agree with the effectiveness and importance         |
| Singapore <sup>28,29</sup> | Compulsory CE  | 50 CE points per 2 years       | Provided by accredited providers, related to pharmacy profession         | Agree with the effectiveness and importance         |
| Japan <sup>8,31</sup>      | Voluntary CPD  | No requirements                | Provided by accredited providers   | Not available                                       |

and Japan, community pharmacists used to spend majority of working hour on dispensing prescriptions. Until recent years, patient-centered pharmaceutical care becomes increasingly significant, community pharmacists start to put more effort on patient counselling. In Hong Kong, similar to Singapore, due to the lack of separation between prescription and dispensing, the role of community pharmacist mainly focus on patient counselling instead of dispensing, indicating the need of broadening pharmaceutical knowledge base should not be inferior to other countries.

As an expert of drug, community pharmacists' knowledge should keep in pace with the development of new diseases and medications. In Hong Kong, including generic products of registered medicines, over 800 drugs are newly registered in 2014, underlining the fast evolution of pharmaceutical knowledge, as well as the need of systematic provision of reliable learning resources for practising pharmacists.<sup>(40)</sup> The fundamental step would be setting up a comprehensive lifelong learning system based on other countries experience.

There is lack of studies comparing the effectiveness or outcomes of mandatory and voluntary lifelong learning programmes. However, existing studies have pointed out the difference in participation rate of pharmacists. In UK, US, Australia and Singapore, lifelong learning is compulsory for re-registration or licence renewal. This means that all the registered and practising pharmacists have to take part in the programme. This is contrasted by the only 10% enrollment of registered pharmacists in the voluntary education system in Japan (statistics in Hong Kong is unknown). To encourage majority of pharmacists to start lifelong learning and attain an overall improvement in pharmacy profession, mandatory lifelong learning system would be a wise choice.

Globally, countries implementing CE or CPD concepts as framework for lifelong learning share certain characteristics:

Firstly, government-accredited learning activities are provided for participating pharmacists. With the exception of UK, in which CPD activities are solely based on pharmacist's individual target and interest, other countries rely on government departments to accredit educational activity providers, such as universities, to offer a range of activities for participating pharmacists. The activities should meet certain criteria before formal recognition. To ensure the consistency the quality of activities, most countries require the activities to contain elements that are practical in workplace and have a link with pharmacy profession and pharmaceutical knowledge. However, there is lack of information about how the activity contents are developed or chosen. Studies should be done annually before courses designation to investigate pharmacists' interests and patients' needs, for example types of diseases that are currently popular in that country, so as to keep the activity contents up to date.

Secondly, for all the countries implementing mandatory CE or CPD system, a minimum number of credits or portfolio entries are required. This can motivate pharmacists to actively participate in lifelong learning, which may result in improvement of the pharmacy profession. However, most of

the currently available studies about the effectiveness of CE or CPD are survey-based and mainly focus on pharmacists' attitude and acceptance. In the coming future, more objective studies need to be conducted, for example compare patient's degree of satisfactory towards pharmacist's pharmaceutical service before and after the implementation of lifelong learning scheme.

Thirdly, pharmacists generally welcome the concept of CE and CPD. However, barriers were identified, indicating the need of improvement in the system.

## FUTURE DIRECTIONS FOR HONG KONG

Based on the cases reviewed, global trend shows the tendency and worthiness for a mandatory pharmacist lifelong learning system. Having a voluntary lifelong learning scheme, a more systemic, impartial and professionally recognised CE or CPD framework is needed in Hong Kong. At this moment, a valuable step would be to investigate the effectiveness of existing programmes as well as the current needs of patients and pharmacists in Hong Kong. Studies need to be done to find out the current pharmacists' interests and practical needs, which would be on first priority for lifelong learning activities development. Data about CE and CPD obtained through this review may serve as a basis for future implementation strategies when the pharmacy profession in Hong Kong decides to head on to this direction.

## CONCLUSION

There is a global shift of role and duty of community pharmacist from traditional dispensing toward patient counselling, which also applies to the situation in Hong Kong. However, with the existing informal voluntary learning programme and some occasional workshops provided by drug companies, Hong Kong is still in the beginning phase of lifelong learning development compared to international trend. A formal and compulsory lifelong learning system is necessary to motivate community pharmacists to further pursue professional knowledge. The first step would be to study the need of patients and the interest of pharmacists in Hong Kong, which provides local statistics for development of lifelong learning activities compatible to local environment. Common features observed from the CE or CPD leading countries in this review article may also serve as a reference for future development of pharmacist lifelong learning framework in Hong Kong.

### Author's background

**HUI, Wynne CW** is currently a Year 3 final year Pharmacy students at the Department of Pharmacology and Pharmacy, The University of Hong Kong. Her email address: [cherryh0210@yahoo.com.hk](mailto:cherryh0210@yahoo.com.hk).

**CHAN, Phoebe WL** is currently a Lecturer at the Department of Pharmacology and Pharmacy, The University of Hong Kong. Her email address: [pwlchan@hku.hk](mailto:pwlchan@hku.hk).

**TAM, Eliza YT** is currently a Lecturer at the Department of Pharmacology and Pharmacy, The University of Hong Kong. Her email address: [eyttam@hku.hk](mailto:eyttam@hku.hk).

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# An Interview of Mr. Mervyn David Loie, a former Chief Pharmacist at the Department of Medical and Health Services, Hong Kong

CHENG, Mary Catherine\*; CHIU, Patrick\*\*

## INTRODUCTION

**Mervyn** Loie joined the civil service as a student dispenser in 1948 and retired as a chief pharmacist of the Department of Medical and Health Services in 1984 after 36 years of service. He was remembered as “Mr. Martindale” for his extensive drug knowledge at work.

To understand more about the Pharmaceutical Services back in 1950s, we organized a meeting with Mervyn Loie in June 2015. The interview of Mervyn David Loie (雷耀光) was a touching story how modern Hong Kong was made by sacrifices of those heroes like himself and his late father; Mr. David Loie (雷福榮).<sup>1</sup>

Mervyn Loie is a loving husband, caring father and a faithful Christian. He started work at a young age of 18, brought up a family of 4 with his wife flourishing in a music career as a world-class soprano cum vocal teacher, a model father to his two sons; Jeff Kai-Wah Loie who is a practising community pharmacist in California, the US and David Man-Wah Loie, a seasoned business executive and a one-time investor in a pharmacy business in Hong Kong.

## THE INTERVIEW

Present: Mervyn David Loie (**ML**雷耀光)

Participants: Mrs. Susan Chi-Ching Loie (nee Poon雷潘志清) (**SL**), David Loie (**DL**雷文華)

Interviewers (**IS**): Mary Catherine Cheng (鄭陳佩華), Patrick Chiu (趙粵)

Date: Saturday, June 6, 2015

Venue: Private residence of Mr. and Mrs. Mervyn Loie

## ON CHILDHOOD and GROW-UP

**IS: Would you like to share with us your family background, childhood and youth days from 1930-1948?**

**ML:** My parents were overseas Chinese originated from Taishan, Guangdong, born and grew up in New Zealand. My late father, David Fook Wing Loie, came to Hong Kong after his graduation from Australia and joined the then colonial government as a Chemical Assistant in 1924.

I am the elder son and had a younger sister in the family. I studied primary school at the Munsang College (民生書院) in Kowloon City and later at the Diocesan Boys' School (拔萃男書院) after WWII. I also attended school in Chongqing (previously called Chung King 重慶), the war time capital of the Republic government of China, for a couple of years in-between.

**IS: What made you travel from Hong Kong to Chongqing during the Japanese occupation?**

**ML:** My grandmother accompanied me to Chongqing, the war time capital of the Republic government of China, with the help of the British Army Aid Group (BAAG).<sup>2</sup> I remembered a long walk each way from our home to the school during the war years when we lived in Chongqing. The area we lived also had other families from Hong Kong.

**IS: Why would BAAG helped you and your grandparents' transfer from Hong Kong to Chongqing then?**

**ML:** Prior to the Japanese occupation, my late father was the government chemist. He was awarded the King's Colonial Police Medal Honour for Gallantry (英皇警察英勇榮譽獎章) posthumously in 1948<sup>3</sup> for his work with BAAG during the Japanese occupation. After my father's sacrifice in May 1943, my grandmother brought me, at the age of 13, immediately to Chongqing at the urge and with the help of BAAG, and we returned a couple of years later when the war ended.

## ON PHARMACY and CAREER

**IS: Did you remember if there were any pharmacies opened then in the 1940s?**

**ML:** I was 10 years old in 1940 and left for Chongqing immediately after my father's death in June 1943. There were many dispensaries and medicine shops selling both western drugs and Traditional Chinese Medicine (TCM) herbs and products in Hong Kong before or during the Japanese occupation.

After Hong Kong was lost to the Japanese on 25 December 1941, some shops selling TCM closed since the availability of herbal remedies from the Mainland became exhausted and no fresh supply was possible. Western medicine was still available but the prices were exorbitant since supply was also limited and came mainly from Japan.

**IS: When did you commence your pharmacy career, and eventually became the chief pharmacist?**

**ML:** I joined the government as a student dispenser in 1948 and registered in the 4-year Chemist and Druggist Certificate Course at the Evening Technical Institute at Morrison Hill, Wanchai. I worked under Ms. Ulian Khoo (邱幼蓮), a tall slim lady pharmacist born in Kuala Lumpur, Malaysia, and learnt dispensing skills in mixing and compounding of medicines at the Queen Mary Hospital, the teaching hospital of the University of Hong Kong, and also pharmacy subjects from Thomas Mahon, an Australian qualified pharmacist, who came to Hong Kong from Fiji Island in 1947 as the chief pharmacist.

I passed the Chemist and Druggist Certificate Examination in 1952 and registered as a pharmacist that year. As I liked the work in hospital pharmacy and despite the salary was higher in the private sector, I stayed on and was appointed as a dispenser in October 1952.

I was transferred to the Kowloon Hospital, and became the pharmacist-in-charge when I was promoted in 1961. A couple of years later, I was transferred to Queen Elizabeth Hospital and was in charge of the pharmacy department when it was opened in September 1963.

In 1972, I was promoted as a senior pharmacist and transferred to the Central Medical Store in Oil Street, North Point responsible for pharmaceutical administration, manufacture and supply of oral liquids, semi-solid dosage forms, and sterile injectables to all government clinics and hospitals. During that time, I had also trained many dispensers in government service and taught pharmacology and dispensing skills.

When Harry Thumb retired in 1977, I was invited to serve as the Acting Chief Pharmacist and then appointed officially as the Chief Pharmacist in 1980 until retirement in 1984.



taken in Manilla, Philippines in 1970s  
(3rd row left) Mr. Mervyn Loie  
(2nd row left 2) Mrs. Josefina Sen, (Centre) Mrs. Susan Loie and  
(Right 2 & 3) Mr. and Mrs. Harry Thumb

|                |  |
|----------------|--|
| 1961           | Pharmacist in charge in Kowloon Hospital   |
| September 1963 | Pharmacist in charge of the Pharmacy Department in Queen Elizabeth Hospital  |
| 1972           | Senior Pharmacist in Central Medical Store in Oil Street, North Point responsible for pharmaceutical administration, manufacture and supply of oral liquids, semi-solid dosage forms, and sterile injectables to all government clinics and hospitals. Also trained many dispensers in government service and taught pharmacology and dispensing skills. |
| 1977           | Acting Chief Pharmacist  |
| 1980 to 1984   | Chief Pharmacist of the Pharmaceutical Service of the Medical and Health Department  |

**IS: How did you find civil service after serving 36 years from the end of WWII to the time when the “Sino-British Joint Declaration on the Question of Hong Kong” was signed in December 1984?**

**ML:** I had the opportunity to serve in the civil service soon after WWII and was part of a pharmacy team to oversee its rapid expansion from 1950s to 1980s. We had a very tight budget to manage and provided an efficient and effective pharmaceutical service to the public during the period of rapid population

growth from 1.8 M to 5 M population. A very meaningful job to serve the community.

**IS: What are your comments with a nick-name “ Mr. Martindale” in the pharmacy profession?**

**DL:** What is the meaning of Martindale? (PC clarified that “Martindale – The Extra Pharmacopeia” is a complete reference guide of drugs). The nick-name of “ Mr. Martindale” was circulated by some government pharmacists who showed their admiration of ML's extensive drug knowledge.

**ML:** I liked to read and write as well as play bridge since these are my hobbies until now. I guessed I had a good memory when I was young. My wife called me a “bookworm” at home. (All laugh).

## ON FAMILY

**IS: Would you like to talk about your family members?**

**ML:** I knew my wife, Susan, since I was a kid as our family elders founded the Chinese Christian Eternal Grace Church (中國基督徒恆恩會) in Tokwawan, Kowloon in the 1930s. We got married in 1952 soon after I became a qualified pharmacist. She is a passionate musician and a soprano cum vocal teacher and was very active in the local music scene. We have two sons; Jeff Kai-Wah (雷啟華) and David Man-Wah (雷文華) .



David, Mervyn, Susan and Jeff Loie Family in the 1960's

Jeff is a pharmacist working in the community in California, the US. David graduated in business management at the University of Strathclyde, in the UK, and he is an amateur pianist and often partnered with my wife on stage.

**SL:** I knew Mervyn when I was small and we played at the Sung Wong Toi Garden (宋王台公園) in Ma Tau Wai, a relic where the last Emperor of Song Dynasty was located, in the early 1930's and 40s but he was always glued to his book. ML had excellent memory and remembered everything.

Mervyn has been a wonderful husband, and he supported my passion in singing and to become a soprano, and took care of the two teenage boys when I went to Italy for three years to learn from the world's greatest female soprano, Madam Maria Canigli, in the 1960's.

**DL:** When I returned from the UK in the mid-1980s, I thought it would be a great idea to open a pharmacy shop with my father as an advisor, after his retirement from the government in 1984, and served the neighbourhood with a purpose.

But we had to close within a year as community pharmacy was a different game if you were to practise in an ethical way since there were few prescriptions issued by private practice medical practitioners.

Simply by relying on the sales of toiletries or OTC medicine would not allow you to make enough margins to pay for the rental of the shop let alone the overheads including the salaries of the pharmacy staff.

**DL:** Jeff's wife, Joceylin Rowan (劉穎珩), my sister-in-law, was the fourth and last daughter of Arthur Rowan (劉仲麟)<sup>4</sup> Joceylin's sister, Geraldine Rowan (劉穎璋), was also a former government pharmacist in Hong Kong.



Mr. and Mrs. Mervyn Loie at their 50th Wedding Anniversary and Family

## CONCLUSION

Mervyn Loie has dedicated his life to public service and pharmaceutical services in Hong Kong. In the 1960's, He worked in the pharmacy department of Kowloon Hospital and Queen Elizabeth Hospital and was responsible for the manufacturing and supply of the drugs to the government clinics and hospitals in the 70's. With his drug knowledge and dedication, he has taught and trained many dispensers for the government hospitals and clinics. Through his story, we have a better understanding of the development of the pharmacy service in Hong Kong from the 1950's to 1980's.

### Author's background

**\*CHENG, Mary Catherine** was the president of the Pharmaceutical Society of Hong Kong (PSHK) from 2012-2014 and is currently a Council Member of PSHK. Mary graduated with a B.Sc. Pharmacy degree from the University of Wisconsin, Madison, U.S. and has practiced pharmacy in Alberta, Canada prior to her return to Hong Kong to join the Department of Health in 1987. Mary was the Assistant General Manager (Quality Assurance) at Eu Yan Sang (Hong Kong) Limited from March 2007 to May 2015.

**\*\*CHIU, Patrick** graduated with a B.Sc. Pharmacy degree at De Montfort University, Leicester, and also with a MBA degree at the University of Hull, Hull, England. He has practised in community, and hospital pharmacy in Britain, Canada, and Hong Kong in his earlier career. Patrick has worked in the pharmaceutical, medical device and clinical laboratory businesses in the Asia Pacific region in the past 30 years. Currently, Patrick is the Managing Director of NPTY China based in Beijing.

### Endnotes:

1. David Loie (LFW) was born in a Chinese Christian missionary family in New Zealand who attended university in Australia. He joined the colonial Hong Kong government's Department of Medical & Health Services as a Chemical Assistant in 1924, promoted as an Assistant Analyst in 1938, and as a Government Chemist in 1940. He also served as the Assistant Superintendent of the former Royal Hong Kong Auxiliary Police (or known as the Police Reserve before WWII), and was compelled to continue to work for the Japanese during the occupation (*Looking back with pride and glory*. Hong Kong Auxiliary Police History Book, 1914-1997. 12 and family legend).
2. BAAG was a unit under MI9, the British Directorate of Military Intelligence Section 9, which was a department of the War Office between 1939 and 1945. In Hong Kong, it was responsible for gathering enemy intelligence and also in assisting prisoners of war to escape from the Japanese Army's Prisoner-of-War (POW) camps. Lt. Colonel Sir Lindsay Ride (LR), who was then a professor of Physiology at the University of Hong Kong before the Japanese occupation, escaped from the POW camp in Shamsuipo, and became the head of BAAG based in Shaoguan (Previously known as Gujiang 韶關/曲江), Guangdong province, the war time capital of Guangdong province in early 1942.
3. LFW joined the BAAG in March 1942, codename MS, as the head of local military intelligence and established a spy network drawn from those who worked with him at the Police Reserve, reporting directly to LR. LFW was arrested on 31 May 1942 by passing intelligence on the Japanese military forces to LR, and committed suicide immediately upon arrest. (*Looking back with pride and glory*. Hong Kong Auxiliary Police History Book, 1914-1997. 12)

One story was that LWF swallowed a very potent poison embedded in his false tooth, and another story was that he jumped to death from the Supreme Court building to protect his direct reports in the intelligence network. (Family legend)

4. Arthur Rowan (AR), a descendant of a Scottish missionary who arrived in colonial Hong Kong in the 19CE, graduated with a MA degree at Cambridge University, qualified as a pharmaceutical chemist in 1927 in the UK and registered as a pharmacist in Hong Kong in the same year (Register of Pharmacists, Hong Kong Government Gazette, February 22, 1957:307).

AR initially worked at the Colonial Dispensary and later on at the China Dispensary, in 1935. He was a key supplier of western medicine to Dr. Selwyn Selwyn-Clarke (SC), a former Director of Medical and Health Services in Hong Kong prior to the Japanese occupation, who organized the smuggling of drugs to those interned at the POW camps in Hong Kong (Selwyn-Clarke, P.S., (1975), *Footprints, The Memoirs of Sir Selwyn Selwyn-Clarke*, Sino-American Publishing Co., Hong Kong. 83)

After WWII, AR opened his own pharmacy under the name Welling Dispensary at 30-32 Des Voeux Road, Central and was very active in the pharmaceutical circle and became the founding president of the Hong Kong General Chamber of Pharmacies. AR passed away in 1972 and left with four daughters.



dissolution and limits any role of variation in individual gastric pH, it may be the source of dyspepsia associated with dabigatran therapy.<sup>(3)</sup> Furthermore, removal of the drug pellets from the capsule shell results in a 75 % increase in dabigatran etexilate bioavailability, compared to the intact capsule formulation.<sup>(7)</sup> Therefore, modification of this delivery system (chewing, breaking, or opening the capsule) is not recommended.<sup>(7)</sup> Co-administration of dabigatran etexilate with food has no effect on the extent of dabigatran absorption and therefore it may be administered with or without meals.<sup>(3,7)</sup>

Rivaroxaban is absorbed rapidly with oral bioavailability reaching 80–100 % for the 10 mg tablet dose, irrespective of fasting or fed conditions.<sup>(8)</sup> Intake with food did not affect the area under the plasma concentration–time curve (AUC) or maximum plasma concentrations ( $C_{max}$ ) after a 10 mg dose of rivaroxaban. In contrast, the bioavailability of a 20 mg tablet was 66 % under fasting conditions but could approach completeness when administered with food.<sup>(8)</sup> Time to peak concentration is around 2 hours.<sup>(8)</sup>

Apixaban is rapidly absorbed after oral administration, with onset of action and time to peak concentration within 3 to 4 hours after oral administration.<sup>(9)</sup> Food does not affect the absorption of drug and thus it can be administered without regard to meals.<sup>(9)</sup> Oral bioavailability of apixaban is around 50 % for doses up to 10 mg.<sup>(9)</sup>

### Distribution

Low (34–35%) concentration independent binding of dabigatran to human plasma proteins was observed. The volume of distribution of dabigatran is 60–70 L, indicating moderate tissue distribution.<sup>(7)</sup>

Rivaroxaban is highly protein-bound (approximately 92–95 % in vitro) and the binding is reversible.<sup>(4,8)</sup> Serum albumin is the main plasma binding component.<sup>(4,8)</sup> Owing to its high plasma protein binding, rivaroxaban is not expected to be dialyzable.<sup>(4)</sup> Volume of distribution at steady state is approximately 50 L (0.62 L/kg), indicating its low-to-moderate affinity to peripheral tissues.<sup>(4,8)</sup>

The volume of distribution of apixaban is low (21 L), suggesting distribution primarily in blood.<sup>(9)</sup> Approximately 87 % of apixaban is plasma protein-bound.<sup>(9)</sup>

### Metabolism and Elimination

Dabigatran is subject to conjugation forming pharmacologically active acylglucuronides.<sup>(3,7)</sup> It is eliminated in the unchanged form primarily in the urine (85%).<sup>(3,7)</sup> Faecal excretion accounted for around 6%.<sup>(7)</sup>

The pro-drug dabigatran etexilate but not dabigatran is a substrate of P-gp.<sup>(7)</sup> Close clinical surveillance is required when co-administered with strong P-gp inhibitors.<sup>(7)</sup> The following strong P-gp inhibitors are contraindicated: systemic ketoconazole, cyclosporine, itraconazole and dronedarone.<sup>(7)</sup> Concomitant administration of a P-gp inducer is expected to result in decreased dabigatran concentrations and thus should be avoided.<sup>(7)</sup>

Elimination of rivaroxaban proceeds via a dual pathway: renal elimination of unchanged drug (approximately one-third of the dose) and metabolic degradation of the drug.<sup>(4,8)</sup> For those subject to metabolism degradation, rivaroxaban is metabolized by several cytochrome P450 enzymes (CYP3A4/5, CYP2J2)

and CYP-independent mechanisms. Rivaroxaban is also a substrate for P-gp and possibly breast cancer resistant protein (BCRP).<sup>(4,8)</sup>

Co-administration of rivaroxaban with strong inhibitors of both CYP3A4 and P-gp has been demonstrated to give significant increase in AUC of rivaroxaban which may lead to an increased bleeding risk.<sup>(8)</sup> Therefore it is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors.<sup>(8)</sup> Substances strongly inhibiting either CYP3A4 or P-gp or moderate inhibitors of both CYP3A4 and P-gp are expected to increase rivaroxaban plasma concentration to a lesser extent and such increase is not considered clinically relevant.<sup>(8)</sup> Concomitant administration of strong CYP3A4 inducers should also be avoided unless the patient is closely observed for signs and symptoms of thrombosis since it was observed to give a reduced rivaroxaban plasma concentration.<sup>(8)</sup>

Metabolism of apixaban is predominantly catalysed by CYP3A4/5, with a lesser extent via CYP1A2, 2C8, 2C9, 2C19 and 2J2, to inactive metabolites.<sup>(5,9)</sup> More than 50% of the administered dose of apixaban is recovered in faeces while about 25% is recovered in urine, with the parent drug representing approximately half of the recovered dose.<sup>(5,9)</sup> Like rivaroxaban, it is also a substrate of P-gp and BCRP.<sup>(5)</sup>

Although the metabolism of apixaban involves CYP isoenzymes and P-gp, the fact that over 50% of the administered dose of apixaban is excreted as unchanged parent drug reduces the overall metabolic potential for a drug-drug interaction with apixaban.<sup>(5)</sup> Indeed, the use of apixaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir).<sup>(5,9)</sup> No dosage adjustment is needed for apixaban when coadministered with less-potent CYP3A4 or P-gp inhibitors.<sup>(9)</sup> The concomitant use of apixaban with strong CYP3A4 and P-gp inducers reduces plasma apixaban concentration.<sup>(5,9)</sup> They should be administered with caution but no dosage adjustment is required.<sup>(9)</sup>

### CLINICAL EFFICACY AND SAFETY DATA

Dabigatran, rivaroxaban and apixaban differ in terms of the current FDA licensed indications. All three of them are indicated for the prevention of stroke and systemic embolism in non-valvular AF, as well as treatment and prevention of DVT and PE; while for postoperative venous thromboprophylaxis, rivaroxaban and apixaban, but not dabigatran, are indicated for such clinical condition.<sup>(2)</sup>

There are currently no highly powered, head-to-head comparative studies between the newer oral anti-coagulants, thus making any direct comparison between the agents, and the determination of their relative place in therapy difficult. To provide a rough comparison, some relevant information extracted from major clinical trials of the three new oral anti-coagulants is compared here.

#### Postoperative venous thromboprophylaxis

Dabigatran is not indicated for this clinical condition, due to the unfavourable results when compared with conventional LWMH prophylaxis in 4 major studies.<sup>(2,10–13)</sup> In RE-MOBILIZE study, dabigatran 220 mg or 150 mg daily was found inferior to

enoxaparin 30 mg twice daily for prevention of VTE after total knee arthroplasty, with similar rates of bleeding.<sup>(10)</sup> While in RE-NOVATE, RE-NOVATE II and RE-MODEL studies, dabigatran 220 mg or 150 mg was non-inferior to enoxaparin 40 mg once daily with similar bleeding rates in thromboprophylaxis after total hip or knee replacement surgery.<sup>(10-13)</sup>

Both rivaroxaban and apixaban are indicated for postoperative venous thromboprophylaxis.<sup>(2)</sup> The efficacy of rivaroxaban in postoperative venous thromboprophylaxis after total knee or hip replacement surgery was compared in RECORD study.<sup>(17)</sup> Rivaroxaban 10 mg daily was superior to enoxaparin 40 mg once daily for thromboprophylaxis after total knee arthroplasty, with similar rates of bleeding.<sup>(17)</sup>

While for apixaban, the efficacy of apixaban was compared in three phase III clinical trials, ADVANCE-1, ADVANCE-2 and ADVANCE-3, with that of subcutaneous enoxaparin.<sup>(19-21)</sup> It is concluded that in VTE prophylaxis after total knee replacement or total hip replacement surgery, apixaban 2.5 mg twice daily was superior to enoxaparin 40 mg once daily, without increase in bleeding risk.<sup>(19-21)</sup>

### Prevention of stroke and systemic embolism in non-valvular AF

For dabigatran, it was compared with warfarin for prevention of stroke and systemic embolism in non-valvular AF in RE-LY study.<sup>(15)</sup> Dabigatran 110 mg twice daily was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major haemorrhage.<sup>(15)</sup> While dabigatran 150 mg twice daily, as compared with warfarin, was associated with lower rates

of stroke and systemic embolism but similar rates of major haemorrhage.<sup>(15)</sup>

For rivaroxaban, when compared with warfarin in ROCKET AF study, rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism.<sup>(18)</sup> There was no significant difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.<sup>(18)</sup>

For apixaban, two clinical trials, AVERROES and ARISTOTLE, were conducted to compare apixaban with aspirin and warfarin respectively for the prevention of stroke and systemic embolism in patients with non-valvular AF.<sup>(22,23)</sup> Apixaban was more effective for stroke prevention than either aspirin or warfarin in patients with AF, even in patient population with only one additional risk factor for stroke.<sup>(22,23)</sup> Even with a superior efficacy, compared with aspirin, apixaban had a similar risk of bleeding; while compared with warfarin, apixaban had an improved safety profile.<sup>(22,23)</sup>

### Treatment of DVT and PE

In RE-COVER study, dabigatran had a similar efficacy and safety profile compared with warfarin for treatment of acute VTE.<sup>(14)</sup>

In a phase III clinical trial EINSTEIN involving rivaroxaban, it had non-inferior efficacy compared with conventional therapy with enoxaparin plus a vitamin K antagonist with similar safety profile in acute treatment of VTE.<sup>(16)</sup> While in continued treatment, VTE risk was lower with rivaroxaban than placebo while the rate of non-major bleeding was higher with rivaroxaban.<sup>(16)</sup>

| Table 1. Summary of clinical efficacy and safety data of dabigatran, rivaroxaban and apixaban  |   |  |  |
|--|---|--|--|
|  | Dabigatran (Pradaxa®)   | Rivaroxaban (Xarelto®)   | Apixaban (Eliquis®)  |
| <b>Mechanism of action</b> <sup>(2)</sup>  | Direct thrombin inhibitor   | Direct factor Xa inhibitor   | Direct factor Xa inhibitor   |
| <b>FDA licensed indication</b> <sup>(2)</sup>  | Prevention of stroke and systemic embolism in non-valvular AF   |  |  |
|  | ✓   | ✓  | ✓  |
|  | Treatment and prevention of DVT and PE  | ✓  | ✓  |
|  | Postoperative venous thromboprophylaxis   | X  | ✓  |
| <b>Clinical efficacy and safety</b>  | <b>Prevention of stroke and systemic embolism in non-valvular AF</b>  |  |  |
|  | <b>RE-LY</b> <sup>(15)</sup> :<br>Dabigatran 110 mg BD was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major haemorrhage. While dabigatran 150 mg BD, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major haemorrhage. | <b>ROCKET AF</b> <sup>(18)</sup> :<br>Rivaroxaban was non-inferior to warfarin for the prevention of stroke or systemic embolism. There was no significant difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.   | <b>ARISTOTLE</b> <sup>(23)</sup> , <b>AVERROES</b> <sup>(22)</sup> :<br>Apixaban was more effective for stroke prevention than either aspirin or warfarin. Even with a superior efficacy, compared with aspirin, apixaban had a similar risk of bleeding; while compared with warfarin, apixaban had an improved safety profile.                                 |
|  | <b>Treatment and prevention of DVT and PE</b>   |  |  |
|  | <b>RE-COVER</b> <sup>(14)</sup> :<br>For treatment of acute VTE, dabigatran had a similar efficacy and safety profile compared with warfarin.   | <b>EINSTEIN</b> <sup>(16)</sup> :<br>In acute treatment of VTE, rivaroxaban had non-inferior efficacy compared with conventional therapy with enoxaparin plus a vitamin K antagonist with similar safety profile. While in continued treatment, VTE risk was lower with rivaroxaban than placebo while the rate of non-major bleeding was higher with rivaroxaban. | <b>AMPLIFY</b> <sup>(25)</sup> , <b>AMPLIFY-EXT</b> <sup>(24)</sup> :<br>In treatment of VTE, apixaban alone was non-inferior to conventional therapy and was associated with significantly less bleeding. While in extended anticoagulation, apixaban at either 5 mg or 2.5 mg reduced the risk of recurrent VTE without increasing the rate of major bleeding. |
|  | <b>Postoperative venous thromboprophylaxis</b>  |  |  |
| <b>RE-MOBILIZE</b> <sup>(10)</sup> :<br>Dabigatran was inferior to enoxaparin 30mg BD for prevention of VTE after total knee arthroplasty, with similar rates of bleeding.<br><b>RE-NOVATE</b> <sup>(11)</sup> , <b>RE-NOVATE II</b> <sup>(12)</sup> , <b>RE-MODEL</b> <sup>(13)</sup> :<br>Dabigatran was non-inferior to enoxaparin 40mg QD with similar bleeding rates in thromboprophylaxis after total hip or knee replacement surgery. | <b>RECORD</b> <sup>(17)</sup> :<br>Rivaroxaban was superior to enoxaparin 40mg QD for thromboprophylaxis after total knee arthroplasty, with similar rates of bleeding.   | <b>ADVANCE-1</b> <sup>(19)</sup> , <b>ADVANCE-2</b> <sup>(20)</sup> , <b>ADVANCE-3</b> <sup>(21)</sup> :<br>Apixaban was superior to enoxaparin 40 mg daily for thromboprophylaxis in total hip or knee replacement surgery, without increase in bleeding risk.  |  |

There were two related phase III clinical trials for apixaban. For treatment of VTE, AMPLIFY was conducted to compare apixaban with conventional therapy.<sup>(25)</sup> For extended VTE treatment, apixaban was compared with placebo in AMPLIFY-EXT.<sup>(24)</sup> In treatment of VTE, apixaban alone was non-inferior to conventional therapy and was associated with significantly less bleeding.<sup>(25)</sup> While in extended anticoagulation, apixaban at either a treatment dose (5 mg) or a thromboprophylactic dose (2.5 mg) reduced the risk of recurrent venous thromboembolism without increasing the rate of major bleeding.<sup>(24)</sup>

A summary of the related clinical efficacy and safety data is shown in Table 1.

## GUIDELINE AND RECOMMENDATIONS FOR DRUG SELECTION

### Prevention of stroke and systemic embolism in non-valvular AF

According to 2014 AHA/ACC/HRS Atrial Fibrillation Guideline, for patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHAD<sub>2</sub>S<sub>2</sub>-VAS<sub>c</sub> score of 2 or greater, oral anti-coagulants are recommended.<sup>(26)</sup> Options include: warfarin (INR 2.0 to 3.0) (Level of Evidence: A), dabigatran (Level of Evidence: B), rivaroxaban (Level of Evidence: B) or apixaban (Level of Evidence: B).

2012 ACCP Antithrombotic Therapy for Atrial Fibrillation recommended that at high risk of stroke (e.g. CHADS<sub>2</sub> score ≥2), use of oral anticoagulation rather than no therapy, aspirin, or combination therapy with aspirin and clopidogrel are recommended.<sup>(27)</sup> When recommending in favour of oral anticoagulation, dabigatran 150 mg 2 twice daily rather than adjusted-dose vitamin K antagonist therapy is recommended.<sup>(27)</sup>

### Treatment and prevention of DVT and PE

According to 2012 ACCP Antithrombotic Therapy for VTE Disease, for acute DVT or pulmonary embolism (PE), initial parenteral anticoagulant therapy (Grade 1B) or anticoagulation with rivaroxaban are recommended.<sup>(28)</sup> For long-term therapy, LMWH or vitamin K antagonists are suggested over dabigatran or rivaroxaban (Grade 2B).<sup>(28)</sup>

### Postoperative venous thromboprophylaxis

According to 2012 ACCP Antithrombotic Therapy and Prevention of Thrombosis, in patients undergoing total hip replacement surgery or total knee replacement surgery, use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis is recommended: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted-dose vitamin K antagonist, aspirin (all Grade 1B).<sup>(29)</sup>

## CONCLUSION

As the members of new oral anti-coagulants, dabigatran, rivaroxaban and apixaban have been shown to have a more favourable pharmacokinetic profile, with comparable or even superior efficacy and safety data when compared to traditional choices. With the increasing support from relevant international guidelines, the use of new oral anti-coagulants is expected to become more popular.

### Author's background

**YIP, Chara Yin-wa** obtained her bachelor degree in Pharmacy in the University of Hong Kong. She is currently a resident pharmacist working in Queen Mary Hospital. Her corresponding e-mail address is [yyw643@ha.org.hk](mailto:yyw643@ha.org.hk).

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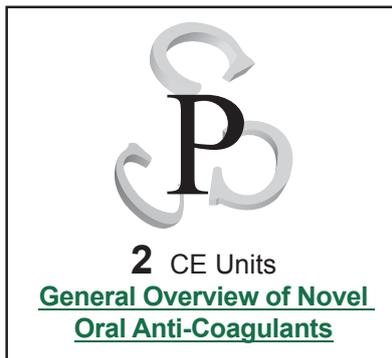
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# Questions for Pharmacy Central Continuing Education Committee Program

( Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)

**1. Regarding the mechanisms of actions of NOACs, which of the following statement(s) is/are correct?**

- (1) Rivaroxaban exerts its anticoagulant effect by inhibiting factor IIa and factor Xa.
  - (2) Dabigatran, of which the prodrug is dabigatran etexilate, is a direct thrombin inhibitor.
  - (3) Dabigatran, rivaroxaban and apixaban have the same mechanism of action.
- A. (1) only  
B. (2) only  
C. (3) only  
D. None of the above



**2. Which of the following statement best describe the absorption of dabigatran?**

- A. Removal of the drug pellets from the capsule shell results in a 75 % decrease in dabigatran etexilate bioavailability, compared to the intact capsule formulation.
- B. Dabigatran is absorbed rapidly with oral bioavailability reaching 80–100 % with empty stomach.
- C. Dabigatran etexilate is packaged in capsules containing both drug and tartaric acid so that it improves drug dissolution and limits any role of variation in individual gastric pH.
- D. The capsules of dabigatran etexilate can be opened if necessary for delivery.

**3. Which of the following is NOT the substrate of P-glycoprotein?**

- A. Dabigatran
- B. Dabigatran etexilate
- C. Rivaroxaban
- D. Apixaban

**4. Which of the following regimen has the lowest potential of drug interaction?**

- A. Dabigatran, erlotinib and simvastatin
- B. Rivaroxaban, rifampicin and amlodipine
- C. Apixaban, itraconazole and nifedipine
- D. Dabigatran, cyclosporine and esomeprazole

**5. Which of the following drugs have FDA licensed indication for postoperative venous thromboprophylaxis?**

- (1) Dabigatran
  - (2) Rivaroxaban
  - (3) Apixaban
- A. All of the above  
B. (1) and (2) only  
C. (2) and (3) only  
D. (1) and (3) only

**6. Which of the following statement concerning efficacy and safety data of NOACs is correct?**

- A. Dabigatran was superior to enoxaparin 30mg BD for thromboprophylaxis after total knee arthroplasty, with similar rates of bleeding.

- B. With a superior efficacy, compared with aspirin and warfarin, apixaban had a similar risk of bleeding in prevention of stroke and systemic embolism in non-valvular AF.
- C. Rivaroxaban was superior to enoxaparin 40mg QD for thromboprophylaxis after total knee arthroplasty, with higher rates of bleeding.
- D. Dabigatran 150 mg BD, as compared with warfarin, was associated with lower rates of stroke and systemic embolism in prevention of stroke and systemic embolism in non-valvular AF.

**7. According to 2014 AHA/ACC/HRS Atrial Fibrillation Guideline, for patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHAD<sub>2</sub>S<sub>2</sub>-VASc score of 2 or greater, which of the following anticoagulants are recommended?**

- (1) Warfarin (INR 2.0 to 3.0)
  - (2) Dabigatran
  - (3) Rivaroxaban
  - (4) Apixaban
- A. (1), (2) and (3) only  
B. (1), (2) and (4) only  
C. (2), (3) and (4) only  
D. All of the above

**8. Which of the following is NOT the advantage of using apixaban instead of warfarin in the prevention of stroke and systemic embolism in non-valvular AF?**

- A. Less frequent blood tests are required for apixaban compared with warfarin.
- B. Apixaban is more suitable for a patient who is concurrently taking voriconazole.
- C. Apixaban was shown to be more effective for stroke prevention with an improved safety profile compared with warfarin.
- D. Apixaban is more suitable for an 80 year-old man who finds it very difficult to follow the diet restrictions of warfarin.

**9. Which of the following anticoagulant is most suitable for an AF patient with prosthetic valve?**

- A. Warfarin
- B. Dabigatran
- C. Rivaroxaban
- D. Apixaban

**10. Which of the following counseling point would you provide to a patient who is newly started on dabigatran?**

- A. Diet restrictions are essential to make sure the intake of vitamin K is consistent.
- B. It is a must to take dabigatran after meal as food increases absorption of dabigatran.
- C. Chewing, breaking, or opening the capsule is not recommended. It has to be swallowed whole.
- D. Routine blood test of measuring INR is essential for monitoring the level of dabigatran.

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 221(D&T)

Warfarin and Analgesics – How Safe is Concurrent Use?

1. B    2. C    3. A    4. C    5. D    6. C    7. A    8. D    9. B    10. D

# SUCRATE<sup>®</sup> gel

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**Actively treat GERD & Gastritis with lesser early relapse  
Heal damaged G.I. lesions & promote complete recovery**

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Gastro-esophageal reflux disease (GERD), gastritis and peptic ulcers of various origin

## Composition

Per 5ml sachet containing 1 gram of sucralfate gel

## Product mechanism and features

Not offered by any Proton Pump Inhibitors, H2-blockers or other acid suppressing agents, Sucrate Gel uniquely forms a cyto-protective layer on the inflamed and damaged mucosae of the G.I. tract. This layer prevents stomach acid, pepsin and bile salts from further eroding the ulcerated tissues. Also, Sucrate Gel stimulates the production of endogenous tissue growth factors (epidermal growth factor, fibroblast growth factor, transforming growth factor alpha, platelet derived growth factor), which promote cell regeneration and angiogenesis.

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- Patented gel form with double surface area of bio-adhesion to ulcerated G.I. tissues
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- Easily swallowed with good tolerance

## Dosage

One sachet 2-4 times a day, according to physician's judgement.

## Manufacturer & origin

Product of Lisapharma S.p.A., Italy.

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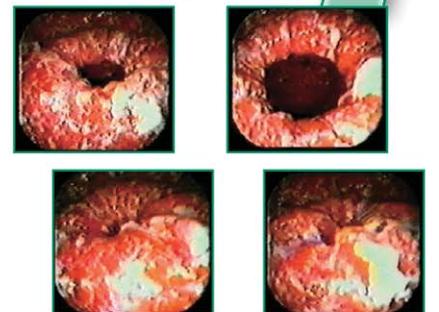
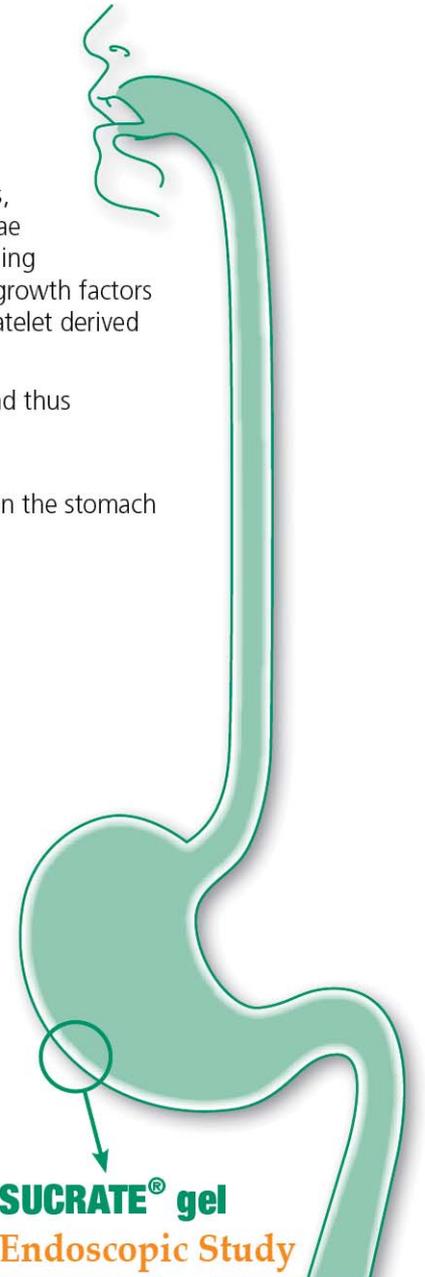
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Cosentino F. et al., Società Italiana di Endoscopia Digestiva, VII Simp. Naz, Napoli, 1992

## A Brief Review on Clinical Data of Nutraceuticals Claiming to Treat Erectile Dysfunction

LAO, Cheng-Kin\*; FONG, Pedro; TONG, Henry Hoi-Yee

School of Health Sciences, Macao Polytechnic Institute, Rua de Luis Gonzaga Gomes, Macao SAR, CHINA  
 (\* Corresponding author; Tel: +853 8599 3473; Fax: +853 2875 3159; Email: cklao@ipm.edu.mo)

### ABSTRACT

Despite the availability of effective drug treatments, nutraceuticals are popular among patients with erectile dysfunction because they are generally considered safe and readily available without a prescription. However, the use of nutraceuticals for this condition is often based on anecdotal evidence. This article reviews the clinical efficacy of seven nutraceuticals claiming to treat erectile dysfunction. Current evidence demonstrates that the efficacy of monotherapy with yohimbine, L-arginine, dehydroepiandrosterone or Maca remains questionable. In contrast, Panax ginseng and the combination of pycnogenol and L-arginine show promising beneficial effects on erectile function. Propionyl-L-carnitine may be useful as an adjunct in patients who do not respond well to phosphodiesterase type 5 inhibitors. It is important for healthcare professionals to provide evidence-based information about the efficacy and safety of nutraceuticals. More well designed studies are needed to confirm their beneficial effects in the treatment of erectile dysfunction.

**Keywords:** Dehydroepiandrosterone, erectile dysfunction, L-arginine, Maca, nutraceutical, Panax ginseng, propionyl-L-carnitine, pycnogenol, yohimbine

### INTRODUCTION

Normal penile erection involves a combination of vascular smooth muscle responses and neurotransmission. Nitric oxide (NO) is believed to be one of the key mediators in the process. Upon sexual stimulation, NO is released by the cavernosal endothelium and nonadrenergic, noncholinergic (NANC) neurons, triggering the relaxation of penile smooth muscles through an increased production of cyclic guanosine monophosphate (cGMP) and a series of intracellular biochemical reactions. Consequently, the sinusoids, which are surrounded by the smooth muscles, are rapidly filled with blood. The expanded sinusoids compress the subtunical venous plexuses and almost completely occlude venous return. These events trap the blood within the corpora cavernosa, leading to penile erection. After ejaculation or loss of desire, cGMP is degraded by phosphodiesterase type 5 (PDE5), returning the penis to the flaccid state.<sup>(1,2)</sup>

Erectile dysfunction (ED) is defined as 'the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance.'<sup>(3)</sup> It can be categorised as organic (neurogenic, hormonal, arterial, cavernosal, or drug-induced), psychogenic or of mixed aetiology.<sup>(2)</sup> ED is often comorbid with a variety

of chronic conditions such as depression, cardiovascular diseases, hypertension, hyperlipidaemia, chronic kidney disease, diabetes mellitus, and other endocrine disorders.<sup>(1,2,4-6)</sup> Age and smoking are also major risk factors for ED.<sup>(2,7)</sup> It should be addressed as early as possible because it can significantly impair the quality of life and psychological well-being of patients and their partners.<sup>(4)</sup>

ED has been a common health issue worldwide, particularly in Asia. A meta-analysis revealed that the prevalence of ED varied widely across Asian countries, ranging from 2% to 81.8%. In China, the overall reported prevalence was between 19.5% and 28.3% in the general population.<sup>(8)</sup> According to a population-representative survey, 36.7% of men aged 26 to 70 years suffered from ED in Hong Kong.<sup>(9)</sup> A recent study reported a much higher prevalence (68%) of ED in the primary care setting.<sup>(7)</sup> As the current first-line therapy, PDE5 inhibitors enhance the penile smooth muscle relaxation and blood flow by reducing the breakdown of cGMP. Their efficacy rates range from 56% to 84% for ED of various aetiologies.<sup>(10)</sup> Despite the availability of effective treatment options (**Table 1**), the majority of patients with ED are reluctant to consult their physicians about the condition.<sup>(11,12)</sup> Based on the results of a global survey, 89% and 85% of people with sexual dysfunction did not seek help from their physicians in China and Hong Kong, respectively.<sup>(13)</sup> Under-reporting of ED is likely due to embarrassment, limited access to care, inappropriate perception of the problem, as well as concern about the safety of Western medicine.<sup>(12,13)</sup>

|                     |   |
|---------------------|---|
| First-line therapy  | Phosphodiesterase type 5 inhibitors:<br>Sildenafil, Tadalafil, Vardenafil, Avanafil |
|                     | Alternative first-line therapy:<br>Vacuum erection devices                          |
| Second-line therapy | Intracavernous injections:<br>Alprostadil, Papverine, Phentolamine                  |
|                     | Intraurethral alprostadil   |
| Third-line therapy  | Penile prosthesis implantation  |

Nowadays, many patients with ED prefer to seek help from the internet rather than healthcare professionals.<sup>(12)</sup> As there is a vast amount of information about complementary and alternative medicine (CAM) available on the internet, it is not surprising that a significant proportion of ED patients opt for nutraceuticals and/or traditional Chinese medicine as their initial treatment.<sup>(12)</sup> Thus, the aim of this review is to summarise the current clinical evidence on the efficacy of seven widely used nutraceuticals that claim to treat ED (**Table 2**). It should be noted that female sexual dysfunction and the other types of sexual problems in men such as premature ejaculation are out of the scope of this review.

## YOHIMBINE

Before the advent of PDE5 inhibitors, yohimbine used to be one of the most prescribed substances for ED treatment in the world.<sup>(14)</sup> It is an alkaloid derived from the bark of the yohimbe tree, a tall evergreen that grows in Africa (**Figure 1**).<sup>(14,35)</sup> Yohimbine is an  $\alpha_2$ -adrenergic antagonist that can reduce the erection-inhibiting impulses in the brain. In the periphery, it can counteract the vasoconstriction caused by the release of norepinephrine and epinephrine in the penile arteries.<sup>(14)</sup> Moreover, *in vitro* data have suggested that yohimbine can enhance NO release from the cavernosal endothelium.<sup>(14,15)</sup>

The vast majority of clinical studies of yohimbine were conducted one to two decades ago when there were no standard methods for assessing subjective erectile function. A meta-analysis of seven randomised, placebo-controlled trials (n=419) concluded that yohimbine monotherapy (5-10 mg three times daily) was significantly better than placebo.<sup>(36)</sup> However, the response rates of yohimbine were only 34% to 73%, as opposed to 9% to 45% in the placebo group.<sup>(37-43)</sup> To date, there has been only one published study that evaluated the efficacy of yohimbine monotherapy by using the 'gold standard' measure, the International Index of Erectile Function (IIEF). The IIEF is a well-validated, multi-dimensional self-report instrument recommended for use in clinical trials of



**Figure 1.** Photos of a yohimbe tree (Left) and the bark (Right). Reprinted from: (Left) Yohimbine medical uses, health benefits and side effects. Medical Health Guide. Retrieved March 12, 2015, from <http://www.medicalhealthguide.com/herb/yohimbe>. (Right) Seigler DS. (2003). Medicinal plants. Retrieved March 12, 2015, from <http://www.life.illinois.edu/ib/363/mediplantslide.html>.

ED, with a high score representing more satisfactory sexual function.<sup>(44)</sup> In the crossover trial including 45 ED patients, the on-demand use of yohimbine (6 mg) one to two hours before sexual activity produced similar results to placebo in all of the IIEF domains including erectile function and intercourse satisfaction (**Table 3**).<sup>(45)</sup> Due to the mixed evidence, the current guideline from the American Urological Association does not recommend its use in the management of ED.<sup>(35)</sup>

**Table 2. Selected nutraceuticals for the management of erectile dysfunction and their proposed mechanisms of action**

| Nutraceutical                                       | Nature and origin  | Proposed mechanism of action  |
|---|--|---|
| Yohimbine <sup>(14,15)</sup>                        | A natural alkaloid derived from the bark of the yohimbe tree | Antagonizing $\alpha_2$ -receptors centrally to reduce erection-inhibiting impulses and peripherally to counteract vasoconstriction in penile arteries; Increasing NO release from cavernosal endothelium |
| Panax ginseng <sup>(16-21)</sup>                    | A perennial plant native to China and Korea                  | Inducing NOS to enhance NO synthesis; Antioxidant properties  |
| L-arginine <sup>(22,23)</sup>                       | A semi-essential amino acid                                  | Precursor of NO; Increasing the activity of NOS   |
| Pycnogenol <sup>(24,25)</sup>                       | The bark extract of the French maritime pine tree            | Reducing oxidative inactivation and prolonging the bioactivity of NO; Stimulating endothelial NOS   |
| Dehydroepiandrosterone (DHEA) <sup>(26,27)</sup>    | The most abundant steroid hormone in blood circulation       | Increasing the expression of NOS in endothelial cells; Precursor of testosterone  |
| Propionyl-L-carnitine <sup>(28-32)</sup>            | Derived from lysine and methionine                           | Increasing production of endothelial NO and prostaglandins; Reducing oxidative stress   |
| Maca ( <i>Lepidium meyenii</i> ) <sup>(33,34)</sup> | The root of a plant that grows in the Central Andes of Peru  | Nutritional properties  |

NO: nitric oxide; NOS: nitric oxide synthase

**Table 3. Randomised controlled trials of yohimbine for treating erectile dysfunction<sup>(36,45)</sup>**

| Study                                 | Design                      | Type of ED (n)                             | Treatment (Length)  | Results (primary outcomes)   |
|---------------------------------------|-----------------------------|--|---|--|
| Morales et al. (1982) <sup>(37)</sup> | Partial crossover study, DB | Organic impotence (100)                    | 6 mg of yohimbine TID vs placebo (10 weeks)   | No significant differences in response rates (42.6% with yohimbine vs 27.6% with placebo; $p=0.42$ )   |
| Reid et al. (1987) <sup>(38)</sup>    | Partial crossover study, DB | Psychogenic impotence (48)                 | 6 mg of yohimbine TID vs placebo (10 weeks)   | Higher response rate in yohimbine group (62% with yohimbine vs 16% with placebo; $p<0.05$ )  |
| Riley et al. (1989) <sup>(39)</sup>   | Crossover study, DB         | Mixed aetiology (61)                       | 5.4 mg of yohimbine TID vs placebo (8 weeks)  | Higher rate of good stimulated erections in yohimbine group (36.7% with yohimbine vs 12.9% with placebo; $p<0.05$ )  |
| Susset et al. (1989) <sup>(40)</sup>  | Partial crossover study, DB | Any type of ED (82)                        | 5.4 mg of yohimbine four times daily ( $\uparrow$ to a max. of 42 mg/d) vs placebo (4 weeks)                                | Higher response rate in yohimbine group (14% full response and 20% partial response to yohimbine vs 3 patients with positive responses to placebo)   |
| Mann et al. (1996) <sup>(41)</sup>    | Two parallel groups, DB     | Organic or non-organic aetiology (31)      | 5 mg of yohimbine TID vs placebo (7 weeks)  | <b>Non-organic ED:</b> significant improvement in Clinical Global Impression scale in yohimbine group (60% with yohimbine vs 40% with placebo); <b>Organic ED:</b> no significant differences between yohimbine and placebo groups |
| Vogt et al. (1997) <sup>(42)</sup>    | Two parallel groups, DB     | Without organic or psychologic causes (86) | 10 mg of yohimbine TID vs placebo (8 weeks)   | Higher response rate in yohimbine group (71% with yohimbine vs 45% with placebo)   |
| Rowland et al. (1997) <sup>(43)</sup> | Crossover study, DB         | Any type of ED (11)                        | 5 mg of yohimbine TID, $\uparrow$ to 10 mg TID vs placebo (4 weeks)   | Higher response rate in yohimbine group (73% with yohimbine vs 9% with placebo)  |
| Lebret et al. (2002) <sup>(45)</sup>  | Crossover study, DB         | Any type of ED (45)                        | 6-g L-arginine glutamate + 6-mg yohimbine vs 6-mg yohimbine alone vs placebo, take 1-2 hours prior to intercourse (2 weeks) | Significant improvement in IIEF erectile function domain scores in combination group vs placebo ( $p=0.006$ ); No significant differences in all domains of IIEF between yohimbine alone and placebo ( $p>0.05$ )                  |

ED: erectile dysfunction; DB: double-blind; TID: three times daily; IIEF: International Index of Erectile Function

The adverse events observed with the doses for ED treatment were generally mild and reversible. Yohimbine, especially at much higher doses, may cause increased blood pressure, palpitations, nausea, anxiety, agitation, insomnia, and manic symptoms secondary to its adrenergic activity.<sup>(14,36,46)</sup> Based on case studies, it may also be associated with renal failure or bronchospasm.<sup>(47,48)</sup> It is recommended that severe cardiovascular diseases, psychiatric disorders, hepatic impairment, and difficult-to-treat hypertension be considered contraindications for the use of yohimbine.<sup>(14)</sup>

## PANAX GINSENG

Panax ginseng, also known as Asian ginseng, is a perennial plant native to China and Korea (**Figure 2**). It has been used as a tonic or adaptogen for improving physical performance and promoting vitality in East Asia for thousands of years.<sup>(16,49)</sup> It is believed to be beneficial for various conditions such as cancer, cardiovascular diseases, cognitive problems, and erectile dysfunction.<sup>(49)</sup> Ginsenosides, a group of steroid glycosides and triterpene saponins, are regarded as the major active constituents of Panax ginseng.<sup>(16)</sup> Multiple animal studies have shown that ginsenosides can cause relaxation of cavernosal smooth muscles by inducing endothelial nitric oxide synthases (NOS) to increase NO production.<sup>(17-20)</sup> The antioxidant properties of ginsenosides may also play a role in their effects on erectile function.<sup>(21)</sup>



**Figure 2.** Ginseng roots (Left) and a diagram of the plant (Right). Reprinted from: (Left) Hoffmann D. (1996). The complete illustrated holistic herbal: a safe and practical guide to making and using herbal remedies. 1<sup>st</sup> Ed. Element Books Ltd., Rockport, MA. (Right) Cai SQ. (2007). Pharmacognosy. 5<sup>th</sup> Ed. People's Medical Publishing House, Beijing.

Among different types of Panax ginseng, Korean red ginseng is the most studied for treating ED. A systemic review published in 2008 identified six randomised clinical trials that reported the efficacy of Korean red ginseng relative to placebo. Among them, three studies were published in English (**Table 4**), with the rest in Korean. The meta-analysis of these six studies (n=349) found that 58% of ED patients treated with red ginseng experienced marked improvement in erectile function, as compared with 20% in the placebo group.<sup>(50)</sup> The dose regimens varied from 600 mg to 1,000 mg three times daily for 4 to 12 weeks in different studies.<sup>(50-53)</sup> For example, in a double-blind, placebo-controlled, crossover study that included 45 men with ED, significantly higher IIEF scores and penile tip rigidity were reported after an 8-week course of red ginseng treatment (900 mg three times daily).<sup>(52)</sup> Nonetheless, it should be taken into account that the total sample size and the average methodological quality of the studies were too low to draw firm conclusion about its benefits.<sup>(50)</sup> Currently, clinical evidence for the use of other types of Panax ginseng in ED management remains scarce. One multi-centre, double-blind, parallel-group, placebo-controlled study was conducted to assess the effects of standardised Korean ginseng berry (SKGB) extract in 118 men with mild to moderate ED. Compared with baseline data, a small but statistically significant improvement in the IIEF-erectile function scores was observed with the treatment of SKGB (700 mg twice daily) for a period of 8 weeks, whereas there was no differences between the SKGB group and the placebo group.<sup>(54)</sup> On the contrary, another type of Panax ginseng called tissue-cultured mountain ginseng extract (1,000 mg twice daily) resulted in more favourable outcomes than placebo although the randomised trial (n=86) was limited by a high dropout rate (69%) in the placebo group.<sup>(55)</sup>

Relatively few adverse events were recognised in the clinical trials of Panax ginseng. Most cases were mild and rarely led to patient withdrawal.<sup>(49)</sup> The documented adverse effects include headache, insomnia, gastric upset and constipation.<sup>(49,50)</sup> A recent report also described two cases of serious psychiatric disturbances associated with the use of Panax ginseng.<sup>(56)</sup> In spite of the promising efficacy, the recommendation for use of Panax ginseng should be made with caution due to the suboptimal quality of current evidence and the paucity of long-term safety data.

## L-ARGININE

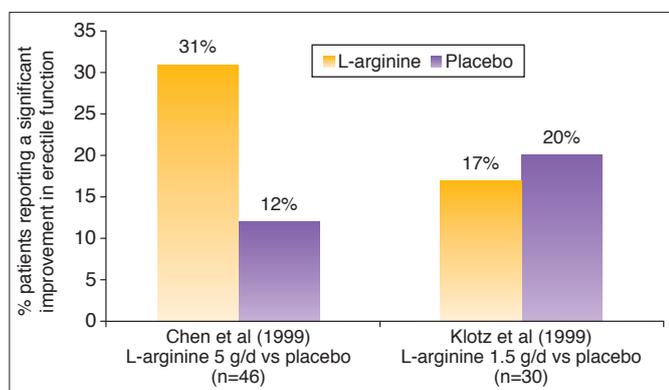
As a semi-essential amino acid, L-arginine plays a crucial role in the proper functioning of cardiovascular, immune, nervous, and endocrine systems.<sup>(23)</sup> It is the physiological substrate for NOS, which facilitates the conversion from L-arginine to NO.<sup>(22,57)</sup> As a result, it has been proposed that oral supplementation

| Table 4. Randomised controlled trials of Panax ginseng for treating erectile dysfunction <sup>(50)</sup> |                           |                     |  |  |
|--|---------------------------|---------------------|--|--|
| Study  | Design                    | Type of ED (n)      | Treatment (Length)                                   | Results (primary outcomes)   |
| Choi et al. (1995) <sup>(51)</sup>   | Three parallel groups, SB | Psychogenic (90)    | 600 mg of KRG TID vs trazodone vs placebo (12 weeks) | Higher response rate in KRG group (60% with KRG vs 30% with trazodone vs 30% with placebo; $p<0.05$ )  |
| Hong et al. (2002) <sup>(52)</sup>   | Crossover study, DB       | Any type of ED (45) | 900 mg of KRG TID vs placebo (8 weeks)               | Higher response rate in KRG group (60% with KRG vs 20% with placebo; $p<0.01$ ); Higher IIEF scores in KRG group (38.1±16.6 with KRG vs 30.9±15.7 with placebo; $p<0.01$ ) |
| de Andrade et al. (2007) <sup>(53)</sup>   | Two parallel groups, DB   | Any type of ED (60) | 1,000 mg of KRG TID vs placebo (12 weeks)            | Higher rate of improvement in KRG group (66.7% with KRG vs 0% with placebo; $p<0.01$ ); Higher total IIEF scores in KRG group (21.0±6.3 with KRG vs 17.7±5.6; $p=0.0002$ ) |

ED: erectile dysfunction; SB: single-blind; DB: double-blind; KRG: Korean red ginseng; TID: three times daily; IIEF: International Index of Erectile Function

of L-arginine may raise the NO levels in the body, which can potentially restore erectile function.

The efficacy of L-arginine monotherapy for ED has been evaluated in three clinical trials. A small pilot study revealed that 40% of patients who had mixed psychogenic and organic ED experienced some benefits after taking L-arginine (2,800 mg/d) for 2 weeks.<sup>(58)</sup> In another double-blind, placebo-controlled trial that included 46 men with organic ED, 31% of the patients treated with L-arginine (5 g/d) reported significant improvement in sexual performance in their diaries, as opposed to 12% in the placebo group. Further objective assessment suggested that high-dose L-arginine therapy may be particularly beneficial in patients with low baseline NO production.<sup>(59)</sup> In contrast, a crossover study completed by 30 men with ED of mixed aetiology showed contradictory results. A 17-day course of low-dose (1.5 g/d) L-arginine treatment was found to be no better than placebo (**Figure 3**).<sup>(60)</sup> It is noteworthy that all of these studies had similar limitations such as small sample size and the use of questionnaires without a well-studied erectile function domain as required by current standards.<sup>(61)</sup> It remains to be elucidated whether L-arginine shows dose-dependent efficacy and is only beneficial for specific types of ED.



**Figure 3.** Subjective outcomes of L-arginine versus placebo for treating erectile dysfunction.<sup>(59,60)</sup>

More recent studies have focused on the effects of L-arginine used in combination with other nutraceuticals. In a double-blind, placebo-controlled, three-way crossover trial (n=45), the IIEF questionnaire was used as the assessment instrument. The study reported that the oral combination of L-arginine glutamate (6 g) and yohimbine hydrochloride (6 mg), given as a single dose one to two hours before sexual intercourse, yielded more improvement in erectile performance than placebo. Theoretically, yohimbine and L-arginine may potentiate the effects of each other.<sup>(45,61)</sup> A subgroup analysis further revealed that the clinical benefits of this combination therapy were limited to patients with mild to moderate ED.<sup>(45)</sup> In addition, a newer combination of L-arginine aspartate (8 g) and adenosine monophosphate (200 mg) was tested in another crossover study (n=26). Based on the IIEF scores, the on-demand use of this combination therapy was superior to placebo in treating mild to moderate ED.<sup>(61)</sup> The clinical evidence of other L-arginine-based combination therapies is listed in the later sections of this review.<sup>(62-66)</sup>

L-arginine exhibits excellent tolerability in clinical trials.<sup>(45,59-61)</sup> One study reported a 10% decrease in systolic and/or diastolic blood pressure associated with L-arginine treatment but it was deemed clinically irrelevant by the authors.<sup>(59)</sup> A few cases of mild gastrointestinal complaints,<sup>(61)</sup>

headache and insomnia<sup>(45)</sup> have been observed with the use of different combination therapies. Unlike PDE5 inhibitors, L-arginine appears to have no significant hypotensive interactions with intravenous nitroglycerin despite its NO-related mechanism of action.<sup>(67)</sup> The efficacy of L-arginine taken alone remains controversial and the evidence supporting the use of combination therapies is limited. More well-designed randomised trials with larger sample size should be conducted to clarify the uncertainty.

## PYCNOGENOL

Pycnogenol is extracted from the bark of the French maritime pine tree (*Pinus pinaster*) (**Figure 4**). It consists of various procyanidins, with phenolic acids as the minor constituents.<sup>(68)</sup> The therapeutic effects of pycnogenol may be attributable to its powerful antioxidant properties. The oxidative stress mediated through superoxide and other reactive oxygen species is believed to be a potential cause of impaired cavernosal function in ED. These reactive oxygen species inactivate NO and thereby impair the relaxation of penile smooth muscles.<sup>(24)</sup> As a radical scavenger, pycnogenol can reduce the oxidative inactivation and prolong the bioactivity of NO. Furthermore, pycnogenol may also increase NO production by stimulating endothelial NOS.<sup>(25)</sup>



**Figure 4.** French maritime pine trees (*Pinus pinaster*) (Left) and the bark (Right).

Reprinted from: *Pinus pinaster*. Wikipedia. Retrieved March 12, 2015, from [http://en.wikipedia.org/wiki/Pinus\\_pinaster](http://en.wikipedia.org/wiki/Pinus_pinaster).

Only one human trial has been conducted to examine the benefits of pycnogenol monotherapy for ED. A double-blind, placebo-controlled study (n=21) showed that pycnogenol (40 mg three times daily) improved ED from moderate to mild levels after 3 months of treatment.<sup>(69)</sup> Conversely, there are much more clinical data on the combined use of pycnogenol and L-arginine, both of which can boost NO levels. In an open-label trial (n=40), only 5% of patients experienced erectile improvement after one month of L-arginine monotherapy, whereas the concurrent use of pycnogenol (80 mg/d) and L-arginine aspartate (3 g/d, equivalent to 1.7 g/d of L-arginine) markedly increased the proportion of recovered patients to 80%.<sup>(64)</sup> The same combination therapy was later evaluated in another placebo-controlled crossover study (n=50) and showed positive efficacy in patients with moderate ED. The mean onset of improvement was 4.9 days, ranging from 1 to 9 days, based on the data from sexual activity diaries.<sup>(65)</sup> The beneficial effects appeared to persist on continuous therapy for up to 6 months.<sup>(66)</sup> Moreover, a small Japanese study (n=23) supported the use of pycnogenol and L-arginine at lower doses for managing Asian patients, especially in enhancing hardness of erection and sexual intercourse satisfaction (**Table 5**).<sup>(63)</sup>

According to the clinical studies, no adverse events were associated with pycnogenol treatment.<sup>(63-66,69)</sup> With respect to the combination therapy with L-arginine, a modest but statistically significant decrease in blood pressure was observed at the end of the treatment.<sup>(63,65)</sup>

## DEHYDROEPIANDROSTERONE

Dehydroepiandrosterone (DHEA) is an endogenous steroid hormone secreted by the adrenal cortex.<sup>(27)</sup> The production of DHEA is age-dependent and peaks between 15 and 45 years of age, followed by a steady decline at a rate of 29% every 10 years.<sup>(70)</sup> Although it is the most abundant steroid hormone in human circulation, its precise physiological role remains unclear. DHEA and its sulphated metabolite, DHEA-S, are the precursors of testosterone and oestradiol. Nonetheless, the peripheral conversion from DHEA and DHEA-S to testosterone may not be significant for men because it only accounts for a tiny part of total testosterone production.<sup>(27)</sup> DHEA is also considered a neurosteroid in the brain<sup>(71)</sup> and it can increase the expression of NOS in endothelial cells.<sup>(26)</sup> It has been suggested that DHEA supplementation may improve mood, cognition, memory, adrenal insufficiency, and female sexual dysfunction although more human data are needed to justify these claims.<sup>(27)</sup>

DHEA and DHEA-S may also be involved in ED. According to the Massachusetts Male Aging Study, there is an inverse correlation between serum DHEA-S levels and the probability of ED.<sup>(72)</sup> The relationship was confirmed by another study showing that ED patients had significantly lower serum DHEA-S levels than healthy volunteers until the age of 60 years.<sup>(73)</sup> Despite the promising findings from observational studies, the interventional studies yielded conflicting results. In a small study (n=30) targeting patients with ED of non-organic aetiology and low serum DHEA-S levels (below 1.5 µmol/L), DHEA supplementation (50 mg/d) was superior to placebo in improving all IIEF domains such as erectile function and intercourse satisfaction.<sup>(74)</sup> An uncontrolled follow-up study (n=80) reported that DHEA use for a period of 6 months was associated with marked erectile improvement from baseline in patients with ED secondary to hypertension and non-organic aetiology, but not in those with diabetes or neurological disorders.<sup>(75)</sup> However, the evidence is far from convincing because of the small sample size of both studies. Furthermore, another placebo-controlled trial which compared DHEA (50 mg twice daily) and testosterone failed to show any clinical responses in 79 men with ED and androgen deficiency.<sup>(76)</sup>

Even though no serious adverse events were reported in most ED-related studies,<sup>(74,75)</sup> DHEA should be used with caution due to its androgenic effects. DHEA treatment can raise serum levels of testosterone in people with androgen deficiency.<sup>(76)</sup> It seems to have no effects on the levels of prostate-specific antigen (PSA) in controlled trials,<sup>(74,76)</sup> whereas previous literature has documented its potential impact on endocrine epithelial cell growth in prostatic tissues.<sup>(77)</sup> It is suggested that DHEA should share the same contraindications and precautions for the use of testosterone replacement therapy.<sup>(27)</sup> In addition, one clinical trial described a case of psychiatric alterations that was considered as probably DHEA-related and led to patient withdrawal.<sup>(76)</sup> Provided that the longest duration of ED-related studies is only 6 months, it is prudent not to recommend long-term use of DHEA for this indication before further efficacy and safety data become available.

## PROPIONYL-L-CARNITINE

Propionyl-L-carnitine (PLC), an amino acid derived from lysine and methionine, is essential in the metabolism of fatty acids and carbohydrates.<sup>(28)</sup> It may be beneficial for cardiovascular diseases, especially peripheral arterial disease.<sup>(78,79)</sup> As ED is strongly linked to cardiovascular diseases and they share similar pathophysiologic mechanisms, PLC may be a viable candidate for ED treatment. Like many other nutraceuticals, the mechanism of action of PLC is not fully understood. Its potential benefits may be due to its ability to improve endothelial dysfunction and blood flow. According to *in vitro* and animal studies, PLC can enhance endothelium-dependent arterial vasodilatation by promoting the synthesis of prostaglandins<sup>(29)</sup> and/or endothelial NO.<sup>(30,31)</sup> The antioxidant properties of PLC may also be a contributing factor.<sup>(28,32)</sup> These proposed mechanisms have been further supported by a clinical study demonstrating a reduction in synthesis of reactive oxygen species and endothelial dysfunction markers such as intracellular adhesion molecule-1 and P-selectin in patients receiving a combination therapy of PLC and sildenafil.<sup>(80)</sup>

Currently, all published clinical trials evaluated the efficacy of PLC as a part of combination therapy or as an adjunct to conventional pharmacotherapy for ED. Most of the studies focused on the patients suffering from both ED and diabetes. Diabetic patients are at three-fold increased risk for ED<sup>(72)</sup> but show a lower rate of responses to PDE5 inhibitors.<sup>(81)</sup> PLC appears to further boost the erectile function when added to the drug regimen in this difficult-to-treat subpopulation. In a study targeting diabetic patients who did not respond to sildenafil alone (n=40), the addition of PLC (2 g/d) to sildenafil

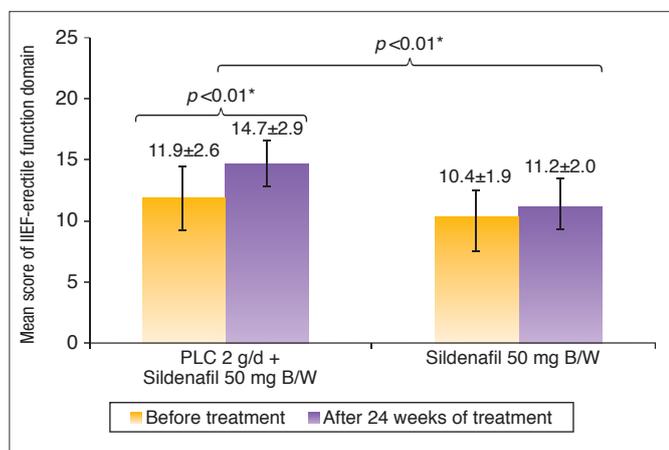
**Table 5. Randomised controlled trials of the combined use of pycnogenol and L-arginine for treating erectile dysfunction**

| Study                                     | Design                  | Severity (n)              | Treatment (Length)  | Results (primary outcomes)  |
|---|-------------------------|---------------------------|---|---|
| Stanislavov et al. (2008) <sup>(65)</sup> | Crossover study, DB     | Moderate ED (50)          | 40 mg of pycnogenol + 1.5 g L-arginine aspartate BID vs placebo (4 weeks)                         | Higher IIEF-erectile function scores associated with the use of combination treatment ( $p < 0.001$ )   |
| Ledda et al. (2010) <sup>(66)</sup>       | Two parallel groups, DB | Mild to moderate ED (111) | 40 mg of pycnogenol + 1.4 g of L-arginine aspartate BID vs placebo (24 weeks)                     | Higher IIEF-erectile function scores in treatment group at 3 months (25.2±2.1 with treatment vs 19.1±3.0 with placebo; $p < 0.05$ ) and at 6 months (27.1±2.1 with treatment vs 19.0±3.1 with placebo; $p < 0.05$ )   |
| Aoki et al. (2012) <sup>(63)</sup>        | Two parallel groups, DB | Mild to moderate ED (23)  | 60 mg of pycnogenol + 690 mg of L-arginine + 552 mg of aspartic acid per day vs placebo (8 weeks) | Higher rate of improvement in treatment group (67% with treatment vs 36% with placebo); Significant improvement in 'hardness of erection' and 'satisfaction with sexual intercourse' from baseline in treatment group ( $p < 0.05$ ); No significant changes in total IIEF scores from baseline in both groups ( $p > 0.05$ ) |

ED: erectile dysfunction; DB: double-blind; BID: twice daily; IIEF: International Index of Erectile Function

(50 mg twice weekly) treatment for 6 months led to marked improvement in achieving and maintaining an erection (**Figure 5**). The successful intercourse rates also rose from 10% to 76% in the combination treatment group.<sup>(82)</sup> The same dose regimen was tested again in another group of diabetic patients and showed similar favourable results.<sup>(60)</sup> More recently, a powdered product of PLC (250 mg/d), L-arginine (2.5 g/d) and nicotinic acid (20 mg/d) was found to be better than placebo in enhancing erectile performance and the combined use of this product with vardenafil was superior to vardenafil alone in diabetic patients.<sup>(62)</sup> With respect to non-diabetic patients, the combination of PLC (2 g/d) and acetyl-L-carnitine (2 g/d) may be beneficial for aged men with partial androgen deficiency<sup>(83)</sup> and may increase the efficacy of sildenafil in restoring sexual potency following retropubic prostatectomy.<sup>(84)</sup>

Based on the current clinical evidence, the addition of PLC to PDE5 inhibitors did not increase the overall incidence of adverse events.<sup>(62,82,84)</sup> PLC may be safely used as an adjunctive therapy in selected patients who do not respond well to PDE5 inhibitors.



**Figure 5.** Clinical outcomes of Propionyl-L-carnitine plus sildenafil versus sildenafil alone for treating erectile dysfunction in patients with diabetes (n=40).<sup>(82)</sup>

PLC: propionyl-L-carnitine; IIEF: International Index of Erectile Function; BIW: twice weekly

\* Statistically significant

## MACA

Maca (*Lepidium meyenii*) is a plant that grows exclusively between 4,000 and 4,500 m above sea level in the central



**Figure 6.** Maca (*Lepidium meyenii*) roots (Left) and a diagram of the whole plant (Right).

Reprinted from: (Left) *Lepidium meyenii*. Wikipedia. Retrieved March 12, 2015, from

[http://en.wikipedia.org/wiki/Lepidium\\_meyenii](http://en.wikipedia.org/wiki/Lepidium_meyenii). (Right) Hernandez Bermejo JE, Leon J. (1994). Neglected crops: 1492 from a different perspective. Food and Agriculture Organization of the United Nations, Rome, Italy.

Andes of Peru (**Figure 6**). It is also known as 'Peruvian ginseng' and has traditionally been used as an energizer or fertility enhancer.<sup>(85)</sup> Maca exhibits favorable effects on spermatogenesis<sup>(86,87)</sup> and sexual desire<sup>(88)</sup> but does not affect serum testosterone levels.<sup>(88,89)</sup> Although the mechanisms of action are largely unknown, the effects of Maca may be partly attributable to its nutritional properties being rich in essential amino acids and minerals.<sup>(34)</sup>

In addition to anecdotal evidence, there is a robust body of animal research showing its benefits for sexual dysfunction.<sup>(90,91)</sup> However, very few human studies have been conducted to evaluate its efficacy for treating ED. In the only clinical trial that included 50 men with mild ED, oral administration of Maca (1,200 mg twice daily) for a period of 12 weeks showed a small but significant improvement in erectile function and subjective well-being, compared with placebo. The enhancing effects of Maca seemed to be inversely related to ED severity prior to treatment. It should be noted that the patients receiving placebo also experienced marked enhancement in erectile function from baseline. Furthermore, the study was limited by the young age of patients (36±5 years).<sup>(33)</sup> More research is needed to support its use for the management of ED.

There have been some safety concerns about one of its constituents named (1R,3S)-1-methyl-1,2,3,4-tetrahydro-beta-carboline-3-carboxylic acid (MTCA). MTCA has been suggested to be a monoamine oxidase (MAO) inhibitor as well as a precursor to mutagenic compounds that may cause neuronal death *in vitro*. Tetrahydro-beta-carbolines may also contribute to craving associated with addiction.<sup>(92)</sup> Nonetheless, Maca is generally well tolerated in clinical trials.<sup>(33,89)</sup> Moreover,

| Table 6. Summary of clinical evidence and safety of selected nutraceuticals for the management of erectile dysfunction |  |   |
|--|--|---|
| Nutraceutical  | Summary of clinical evidence   | Potential adverse effects   |
| Yohimbine <sup>(14,36,45,46)</sup>   | Inconclusive evidence.   | Increased blood pressure, palpitations, nausea, anxiety, agitation, insomnia and manic symptoms |
| Panax ginseng <sup>(49-55)</sup>   | May have modest benefits based on studies of suboptimal quality.   | Headache, insomnia, gastric upset and constipation  |
| L-arginine <sup>(45,58-66)</sup>   | Mixed responses when used alone.   | Decreased blood pressure  |
| Pycnogenol <sup>(63-66,69)</sup>   | Limited data on monotherapy.<br>May be beneficial when used with high-dose L-arginine.   | None reported (monotherapy)   |
| Dehydroepiandrosterone (DHEA) <sup>(74-76)</sup>   | Inconclusive evidence.<br>May be beneficial for patients with non-organic erectile dysfunction and low serum DHEA levels.              | Increased testosterone levels   |
| Propionyl-L-carnitine <sup>(62,80,82-84)</sup>   | No data on monotherapy.<br>May be beneficial as an adjunctive therapy in diabetic patients who do not respond well to PDE5 inhibitors. | Unknown (monotherapy)   |
| Maca ( <i>Lepidium meyenii</i> ) <sup>(33,89)</sup>  | Limited clinical data  | Unknown   |

these potential problems have not been observed in other *in vitro* studies of Maca, leading to the assumption that MTCA may become much less toxic following the boiling preparation process of Maca.<sup>(93)</sup>

## CONCLUSION

ED is a prevalent condition that can have a negative impact on quality of life. In spite of the proven efficacy of PDE5 inhibitors, most men with ED shy away from seeking professional help because of cultural and social factors. Information technology, especially the internet, empowers patients to have a more active role in their own health care. Patients with ED can easily find different information about treatment options. Therefore, the relatively 'safe' nutraceuticals have become increasingly popular. These seven nutraceuticals are among the many products that claim to be effective for treating ED and are readily available at pharmacies, health food stores, and online shops. Nonetheless, a number of nutraceuticals are used primarily based on anecdotal information. It is important for healthcare professionals to make patients aware of the up-to-date evidence on the efficacy and safety of nutraceuticals, so that they can receive the most appropriate treatment. According to current clinical data, the efficacy of L-arginine for treating ED remains inconclusive and may be dose-dependent. Yohimbine should be used with caution due to safety concerns and mixed responses. In addition, the clinical evidence regarding DHEA supplementation is conflicting and can only be applied to ED patients with low serum DHEA levels. Although Maca has been used for enhancing fertility in South America for centuries, its efficacy is only modest for mild ED. In contrast, Panax ginseng monotherapy and the combination treatment of pycnogenol and high-dose L-arginine show promising benefits in clinical trials but more data are necessary to draw a firm conclusion. PLC, often used as a part of combination therapy, may increase the efficacy of PDE5 inhibitors in patients with diabetes (Table 6). It is noteworthy that most clinical studies involving these nutraceuticals are limited by small sample size, significant placebo effects, short treatment duration or other methodological flaws. Before larger, well-designed studies are conducted to confirm their beneficial effects and tolerability, these nutraceuticals should not be advocated as the mainstay of therapy for ED. Moreover, further research is needed to compare the efficacy of these nutraceuticals and conventional pharmacotherapy for ED.

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### Author's background

**Dr. LAO Cheng-Kin** is a lecturer of the School of Health Sciences at the Macao Polytechnic Institute. He graduated from the PharmD program at the University of Kansas and completed pharmacy residency training at the University of California, San Francisco. He has been a Board Certified Pharmacotherapy Specialist since 2010. His email address is: cklao@ipm.edu.mo. **Dr. FONG, Pedro** is a lecturer of the School of Health Sciences at the Macao Polytechnic Institute. He has MPharm and PhD degrees from the University of Manchester. **Dr. TONG Hoi-Yee, Henry** is a professor at the Macao Polytechnic Institute, with adjunct/honorary titles at HKU and HKUST.

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# Study Visit to Beijing and the Forbidden City International Pharmacist Forum 2015

**CHENG, Mary Catherine<sup>a</sup>; CHAN, Ka Lok<sup>b</sup>; CHAN, Mei Ying Mandy<sup>b</sup>; CHAN, Pan<sup>b</sup>; CHAN, Yik Kei<sup>b</sup>; CHENG, Sze Nok<sup>b</sup>; LAM, Chun Sing<sup>b</sup>; LAU, Kai Cheong<sup>b</sup>; LEE, Ka Ki<sup>b</sup>; LEE, Man Huen Isis<sup>b</sup>; LEUNG, Shek Ming<sup>b</sup>; LI, Jiacheng<sup>b</sup>; LI, Yuen Shun Janice<sup>b</sup>; LUI, Yiu Yee<sup>b</sup>; TAM, Lok Pui<sup>b</sup>; YUENG, Ching Ying<sup>b</sup>**

<sup>a</sup> *Pharmaceutical Society of Hong Kong*

<sup>b</sup> *School of Pharmacy, The Chinese University of Hong Kong, Shatin, NT, Hong Kong*

On 7 May 2015, the Pharmaceutical Society of Hong Kong, organized a study visit to 2 hospitals in Beijing and the Forbidden City International Pharmacist Forum. The delegation consisted of 9 pharmacists and 15 pharmacy students. This year, there were 4 speakers attending the Forum, including Prof. Vivian Lee, Dr. Chan Man Chi Grace, Ms. Li Win Man Amanda and Mr. So Kai Him; Mr. Philip Chiu, Mrs. Mary Catherine Cheng, Mr. Benjamin Kwong, Mr. Matthew Wong and Mr. Patrick Chiu also participated in the study visit and attended the Conference.

### VISIT TO PEKING UNIONMEDICAL COLLEGE HOSPITAL (協和醫院)



*PSHK delegation with Ms. Mei Dan at PUMCH*

In the morning of 8 May 2015, the PSHK delegation visited the Peking Union Medical College Hospital. We were provided with a brief introduction of the hospital by Ms. Mei Dan and this hospital has been classified as a Class A Tertiary Comprehensive Hospital. The hospital has been focusing on clinical care, innovative scientific research and medical education. This hospital was even granted the best hospital ranking in China from 2010 to 2014. The most impressive part of this hospital was that the advanced automatic technology. The hospital has achieved high efficiency by adopting automatic dispensing practice. By observing various dispensing machines in the pharmacy, it was believed that the hospital has been willing to invest in automatic dispensing system. The hospital has been relying on efficiency and accuracy



*The automatic dispensing system in PUMCH*

of the system. As a result, the waiting time for the busy pharmacy with over 10000 prescriptions a day has been drastically shortened to 10 minutes and the queue was observed to be short. Patients seemed to be satisfied with the pharmacy performance. The



*The effective dispensing system greatly minimize the waiting time of patients*

The automatic dispensing system has been working well in Peking Union Medical College Hospital, while the public hospitals in Hong Kong have not adopted the system because of some true differences between the two places. For example, the practice in Beijing prefers to dispense the whole boxes of drugs and the duration of drugs dispensed are usually less than one month while Hong Kong public hospitals prefer to dispense the exact number of pills required and very often dispensed up to six months' supply of drugs. It is necessary to shorten the duration of drugs dispensed to patients before automation can be achieved in our Hong Kong Public Hospitals.

Another impressive observation was that there were a lot of proprietary Chinese medicines in the pharmacy. This raised a question that how a Western medicine practitioner prescribed both Western and Chinese medicines to the patients. Interestingly, in one of the talks of The Forbidden City International Pharmacist Forum, the speaker said that over 70% of the proprietary Chinese medicines were prescribed by Western medicine practitioners but not Chinese medicine practitioners. This prescribing practice is quite surprising and further investigation might be useful because a lot of Hong Kong people rely on both Western and Chinese medicines. The combination use of Western and Chinese medicines poses a big challenge to pharmacists.

### VISIT TO BEIJING UNITED FAMILY HOSPITAL (北京和睦家醫院)

We were given a presentation by Ms. Helen Zhang, the Director of Pharmacy of United Family Healthcare, a network with hospitals and other medical facilities in Beijing, Shanghai, Guanzhou, Tianjin, Wuxi and Ulaanbaatar, aims to provide high quality medical services. BJU is comparable to private hospitals in Hong Kong. About 60 and 800 patients use its inpatient and outpatient services every day; half of them

being expatriates so both English and Mandarin are primary languages used in BJU. Emphasizing on evidence-based medicine, integrity, patient care and mutual respect, Ms. Zhang also introduced the cultures and core values of BJU to us. After that, Sabrina Ji, a resident pharmacist, explained the training programme of pharmacy department in BJU to us. Trainees are provided with systematic training, objective evaluation and well-rounded support. It was impressive to us that each trainee has to complete 10,000 dispensing activities that he or she is required to start all over again if any mistakes are made. It sounds harsh but is actually reasonable as any errors in the medical setting can kill.



*PSHK delegation with Ms. Helen Zhang of Beijing United Family Hospital*

Then we had a guided tour around the hospital, including the first two blocks. In the pharmacy, due to the relatively small number of prescriptions, automation and mass dispensing was not used extensively as in Peking Union Medical College Hospital.



*A satellite pharmacy of Beijing United Family Hospital*

BJU uses computerized system for dispensing and keeping patient profiles. At the patient admission and discharge, pharmacists will conduct medication reconciliation respectively to avoid medication error. We also went to the Obstetrics and Gynecology wards and common areas. The environment was very comfortable.



*The VIP room at Beijing United Family Hospital*

## **THE FORBIDDEN CITY INTERNATIONAL PHARMACIST FORUM (FCPF) 2015**

The FCPF from 8th to 10th May 2015 was organized by the China Health Promotion Foundation together with China Pharmaceutical Association, American Society of Health System Pharmacists, 日本病院薬剤師會, 中日醫學科技交流協會, 藥品評價雜誌社 and 藥學工具網. The theme of the 2015 forum was "Expanding the Scope of Pharmaceutical Service and Forging Eight-Star Pharmacists". The forum invited more than 300 experts of medicine and pharmacy from more than 20 countries and places to have talks in sub-forums of 19 themes, such as Pharmacy administration, Pharmaceutical Education,

Medication quality and safety, Working mode of specialized pharmacist, Expanding the scope of pharmaceutical service, Safety and management of biological products, Informatization, automation and information service in pharmacy, medical insurance, pharmacoeconomics and rational drug use, Rational use of TCM, TDM, pharmacogenomics and personalized medicine, Pharmacovigilance and risk management, chronic disease management and pharmaceutical practice,

## **Expanding the Scope of Pharmaceutical Service and Forging Eight-Star Pharmacists (Forum Theme Reflection)**

The Eight Stars mean eight characters a pharmacist should be, which are Caregiver, Decision Maker, Lifelong Learner, Team Player, Leader, Manager, Communicator and Teacher. Douglas J. Scheckelhoff, a pharmacist from US, suggested eight ways to expand the pharmaceutical service, which are developing a safe, effective, efficient distribution system; identifying patient care area or service to be discovered; utilizing existing literature and experience of others; cost consideration; assessing competencies of staffs; placing pharmacists in patient care area; collecting outcome data and documenting pharmacists' activities; and increasing pharmacists' involvement in all settings. To be a pharmacist in Hong Kong, we should chase for being Eight-Star pharmacists.

## **Health insurance, pharmacoeconomics and rational use of drug**

The health care system in China has been undergoing reforms for the past three decades. New policies and regulations are developed to better meet the health needs. Since the life expectancy in China has increased dramatically, health insurance, pharmacoeconomics and rational use of drugs are of paramount importance.

They are facing lots of challenges. Historically, there were two main health insurance systems: the labor insurance schemes and government employee insurance schemes, but about 700 million rural Chinese citizens were health uninsured. On the other hand, in both rural and urban areas, public hospitals are caught in a financial squeeze. The government sets prices for many medical services far below actual costs, to improve affordability of these services, which increase the financial burden of the government.

The Chinese government has implemented a series of new reform measures to address different challenges. Efforts to ensure continuous investment in basic health care infrastructure are likely to help further to reduce urban-rural disparities in resources allocation. For example, the Ministry of Health expanded the national essential drug list, which may further enhance the accessibility and affordability of treatments and help to narrow the gap in medical services provided to urban and rural areas.

Pharmacoeconomics is a part of the health economic outcome research, which can actually help to achieve the rational and cost-effective use of drugs, thus reducing the burden of the government. It is quite interesting that a cost-utility analysis showed that the adjuvant therapy with

capecitabine and oxaliplatin recommended by the Chinese National Comprehensive Cancer Network guidelines was cost-effective for the treatment of resectable gastric cancer patients in the long run but not in the short term, suggesting the importance of considering the long-term economic value of new technology in China's healthcare system.

Pharmacoeconomics plays an important role in the decision making process by promoting the rational, evidence-based, clinically appropriate, safe and cost-effective use of medications, so as to optimize patient care. Different parties should pay efforts to conduct outcome research and facilitate the rational use of drugs.

### Working mode and performance appraisal of specialized pharmacists

There are barriers against education of clinical pharmacists, which are the lack of basic education, serious shortage of clinical pharmacists and the separation of medical services and drugs. Chen Wenying, a pharmacist in China, mentioned that to solve the problems, pharmacists should improve their skills, participation, independent problem solving skills and confidence. Training that includes homework, quiz, daily ward rounds, teaching ward rounds, discussion and communication with patients and doctors are needed.

Another pharmacist, Ge Weihong, mentioned that about 80% of pharmacists are now working at dispensing places. To expand the pharmacy service to clinical department, pharmacists should shift their workplace from dispensing to clinical areas, medication management in surgery, internal medicine management, experiment and research.

After two pharmacists specialized in oncology and nephrology from US and China respectively shared their daily practice, a pharmacist from Malaysia, Sulaiman, talked about how to improve clinical pharmacy practice. Firstly, pharmacists should show their leadership in healthcare team. Secondly, pharmacists need to be mobile and do not just stay in pharmacy, but perform medication review, ward round, therapeutic drug monitoring, clinical trial, pharmacoeconomic study and teaching. Thirdly, pharmacists should document and publish what they have done, including intervention and research. Fourthly, we should be 9-stars pharmacists, with 'researcher' as the extra star, transforming research into clinical knowledge to help patients. Finally, pharmacists need to educate patients about clinical knowledge of their diseases, which can improve their compliance.

Dr. Chan Man Chi, our speaker from Hong Kong gave a talk on "The certification and training of specialized pharmacist in Hong Kong China. Mr. So Kai Him, clinical pharmacist from Hong Kong gave a talk on "The clinical pharmaceuticals service in Hematology and Oncology"



Dr. Chan Man Chi gave the talk on training of specialized pharmacist in Hong Kong



Mr. So Kai Him gave the talk on hematology and oncology

### Rational drug use and practice in special clinic - ophthalmology, gynecology and obstetrics

Nowadays, combined oral contraceptives pills are effective in birth control. However, many women discontinue the contraceptive treatment as they cannot tolerate it. Huang Zirong, a pharmacist from China introduced a new type of oral contraceptives - YAZ. The clinical characteristics of YAZ are that it is a low-dose COCs containing Drospirenone and it has a unique 24/4 regimen instead of the traditional 21/7 regimen. It is proven to have similar efficacy as other high-dose contraceptive pills and it can improve the monthly discomfort due to the shortening of hormone-free interval, therefore improving the tolerance.

Another pharmacist, Li Wing Man Amanda, from Hong Kong introduced the rational drug use in sick children. It is a big challenge in pediatrics as many drug uses in children is off-labeled. For example, there is not many clinical trials done on children, pharmacists need to practice in unknown. Also, the formulation may not be originally for children. Crushing tablets may be needed. As children grow every day, there may be huge change in pharmacokinetics and pharmacodynamics. Therefore the treatment should be individualized. The role of pharmacist is to verify the doctor's prescription and resolve drug-related problems in order to ensure efficacy and safety of patients.



Ms. Amanda Li gave the talk on prescription checking in pediatrics

### Rational use and practice of Traditional Chinese Medicine

In China, besides modern medicine, Traditional Chinese Medicine (TCM) also plays an important role in the healthcare system. Although comparatively TCM has fewer side effects than western pharmaceuticals, irrational use can also lead to toxicity and adverse events. Hence, it is necessary to beware of the safety of use of TCM.

One of the few problems in TCM practice nowadays is the excessive medical prescription, which includes those with large dosage or large amount of herb types used. The disadvantage is that the chemical composition can become very complex that may lead to instability, safety and lowered effectiveness due to interactions. Besides, it would also increase the interactions between TCM and western medicine if the patient is taking both of them. Despite of these, it is necessary to legitimize the use of some prescriptions in literature that belongs to large prescription. Therefore, the safety and effectiveness of these excessive prescriptions have to be balanced, while monitoring has to be carried out during the use of these prescriptions.

Another problem is off-label use of TCM, which is also a common situation for western pharmaceutical products. However, for TCM, the situation is much more prevalent, especially in pediatric, geriatric, pregnancy and as proprietary product. The off-label use can be due to the lack of timeliness and limitation of the product insert, the complexity of the medical situation or the exploration by physicians. In fact, the trial of off-label use can assist the development of use of TCM, but at the same time, can bear a higher risk of patient safety. Questions remain in how the benefits and risk of off-label use can reach a reasonable balance.

Though there are safety challenges with the use of TCM in China, it is appreciated that there is integrated use of TCM and western pharmaceutical products together in many areas of practice to assist patient care. It may also assist the development of optimal patient care in complex disease, like tumors. In fact, pharmacists can have more active role in optimizing the integrated care with TCM and modern medicines, as well as enhancing safe use of medications with rigid monitoring and appropriate intervention through future development of clinical pharmacy in TCM.

### **Therapeutic Drug Monitoring (TDM), Pharmacogenomics and Individualized Medicines**

Owing to individual variability in pharmacokinetic and pharmacodynamic characteristic of different drugs, the currently using model, one size-fits-all pharmacology, which is fueled by "trial and errors", is outdated and no longer the best model. To replace the old-fashioned model is the Genomic Model which advocates pharmacogenetic stratification. Furthermore, Therapeutic Drug Monitoring (TDM) is inevitable and a prerequisite for clinical safety and rational use of drugs, achieving optimal pharmaceutical care. As a result, more studies emerged and were delivered with a bid to enhance safety and accuracy of TDM and developing pharmacogenomics.

A number of drugs were illustrated as examples and discussed in the above-mentioned field. Tamoxifen, which is a selective estrogen receptor modulators and indicated for treatment of breast cancer, is an example mentioned repeatedly in the conference. Tamoxifen would be activated by cytochrome P450 enzyme (CYP2D6) to become active metabolite, endoxifen. However, due to genetic variations among individuals, there are variations in expression of CYP2D6, which results in roughly at least 4 types of patients, namely ultra-rapid metabolizer, extensive metabolizer, intermediate metabolizer and poor metabolizer. As a result, obviously and reasonably, different patients would have different response towards tamoxifen. For example, extensive metabolizers have a longer time to cancer recurrence than intermediate metabolizer and poor metabolizer. It is suggested that poor and intermediate metabolizer may have better therapeutic outcomes with different dose or alternate treatment such as aromatase inhibitors.

### **Clinical pathway, guideline and pharmaceutical practice**

Clinical pharmacists work in a multidisciplinary team, with inter-professional cooperation to perform pharmaceutical practice. They focus on various drug-use strategies in different diseases states after reviewing evidence-based medicines and literatures. The series of lectures under this topic guide the pharmaceutical practice in China from global perspectives.

A speaker illustrated her ideas through taking the new drug therapy guideline in asthma and Chronic Obstructive Pulmonary Disease (COPD) as examples. Using GINA 2014 as reference, the severity of asthma would be divided into different stages through symptom control evaluation. Following the new guideline, there would be different first and secondary drug choices in different asthma disease states. Moreover, there would be some restriction on drug choices. For instance, Tiotropium would only be initiated in stage 4 or 5 of asthma,

the patients were over 18 years old and had the history of exacerbation. These approaches could enhance the quality, efficiency and safety in pharmaceutical practice.

As the speakers said, clinical pathway would become the standard in future development of pharmaceutical care and practice in China. The role of pharmacists would gradually be introduced into clinical area, which could reduce physicians' workload and get involved in professional healthcare cooperation so as to promote patient-centered care.

### **Pharmacovigilance and risk management**

One special part in this topic is talking about clinical safety of traditional Chinese medicine (TCM). TCM has been internationalized and modernized. They have long been regarded as safe and non-toxic. However, are they really safe? There is only a few clinical evidence on the safety of TCM. Therefore, guidance on post-marketing safety of TCM has been published, including types, severity of adverse drug reactions and intervention assessment. The risk is divided into mainly four classes. The aim of risk management in TCM is to reduce the risk to the lowest - the Class I, meaning that information from clinical trial phase I to IV is completed and with post-marketing safety assessment.

Besides working on systematic aspect, the role of clinical pharmacists in pharmacovigilance and risk management was also mentioned. There are mainly three areas a clinical pharmacist can work on, which are education, monitoring and proper medication disposal. For education, both healthcare workers and patients are included. For example, pharmacists can give advice to healthcare providers on rational prescription of opioids and also educate patients how to safely use and store the medications. For monitoring and tracking, there is a program called Prescription Drug Monitoring Program (PDMP) in the US. It is a statewide electronic database which collects designated data on substances dispensed in the state. This database helps pharmacist to monitor the use of medications efficiently. For proper medication disposal, medications should be disposed in a convenient and environmentally-friendly way under pharmacists' control. In this way, the number of prescribed drugs being abused can be reduced.

Pharmacovigilance and risk management can be done on country-based, industry-based and individual-based. The very final goal is to minimize the number of medication errors and ensure that patients use the medications safely.

### **CONCLUSION**

The study visit to the Peking Union Medical College Hospital showed how automation has helped reduce the waiting time in the busy outpatient clinic and the visit to Beijing United Family Hospital demonstrated the high quality medical services available in China. The Forbidden City International Pharmacist Forum 2015 is an eye opening experience for the pharmacy students and for all pharmacists to learn about the new developments in the pharmacy arena worldwide. It also enabled us to foster communication and friendship with pharmacists in China and other countries.

MOMENTS LIKE THIS...

## SOVALDI® transforms HCV therapy, allowing many more patients the opportunity of cure†

- The nucleotide polymerase inhibitor with pan-genotypic activity<sup>1</sup> and a high barrier to resistance<sup>2</sup>
  - ≥90% cure across genotype 1-6 with 12 weeks of SOVALDI + Peg-IFN + RBV in previously untreated HCV mono-infection adults<sup>1\*</sup>
  - An all-oral 24-week option available for those patients unsuitable for Peg-IFN<sup>1\*</sup>
  - No adverse drug reactions specific to SOVALDI<sup>1</sup>
- In the context that SOVALDI has mainly been studied in combination with RBV, with or without Peg-IFN

SOVALDI is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

†The proximate goal of HCV therapy is SVR (virologic cure), defined as the continued absence of detectable HCV RNA at least 12 weeks after completion of therapy.<sup>3,4</sup>

\*12-week all-oral SOVALDI + RBV regimen for GT 2.

 **SOVALDI®**  
SOFOSBUVIR  
400 mg TABLETS  
HCV treatment transformed

### SOVALDI Abbreviated Prescribing Information

**Presentation:** Film-coated tablet containing 400 mg of sofosbuvir. **Indications:** In combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults. **Dosage: Adults:** One 400 mg tablet, taken orally, once daily with food. **Elderly:** No dose adjustment is warranted for elderly patients. **Renal impairment:** No dose adjustment is required for patients with mild or moderate renal impairment. The safety and appropriate dose have not been established in patients with severe renal impairment or end stage renal disease requiring haemodialysis. **Hepatic impairment:** No dose adjustment is required for patients with mild, moderate or severe hepatic impairment. The safety and efficacy have not been established in patients with decompensated cirrhosis. **Patients awaiting liver transplantation:** The duration of administration should be guided by an assessment of the potential benefits and risks for the individual patient. **Paediatric population:** The safety and efficacy in children and adolescents aged <18 years have not yet been established. No data are available. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and Precautions:** Sovaldi is not recommended for administration as monotherapy and should be prescribed in combination with other medicinal products for the treatment of hepatitis C infection. Treatment-experienced patients with genotype 1, 4, 5 and 6 HCV infection; Treatment of patients with genotype 5 or 6 HCV infection; Interferon-free therapy for genotype 1, 4, 5 and 6 HCV infection; Co-administration with other direct-acting antivirals against HCV; co-administration with telaprevir and boceprevir is not recommended. Pregnancy and concomitant use with ribavirin; Use with potent P-gp inducers; Renal impairment; HCV/HBV (hepatitis B virus) co-infection; Paediatric population below age of 18; Women of childbearing potential; Pregnancy and lactation; Moderate influence on ability to drive and use machines. **Undesirable effects:** Sovaldi has mainly been studied in combination with ribavirin, with or without peginterferon alfa. In this context, no adverse drug reactions specific to sofosbuvir have been identified. The most common adverse drug reactions occurring in subjects receiving sofosbuvir and ribavirin or sofosbuvir, ribavirin and peginterferon alfa were fatigue, headache, nausea and insomnia.

**Before prescribing, please consult full prescribing information which is available upon request.**

SOVALDI is a registered trademark of Gilead Sciences, Inc., or its related companies.

Reference: 1. Sovaldi Hong Kong Prescribing Information (EUJAN14HKFEB14). 2. Kris V Kowdley et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naïve patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicenter phase 2 trial. *Lancet* 2013 Mar. 3. AASLD & IDSA. Recommendations for Testing, Managing, and Treating Hepatitis C. 2014 Dec. 4. European Association for the Study of the Liver (EASL). EASL Recommendations on Treatment of Hepatitis C 2015. *Journal of Hepatology*. 2015 Mar.



### Gilead Sciences Hong Kong Limited

Room 2603, 26th Floor, Hysan Place, 500 Hennessy Road, Causeway Bay, Hong Kong  
Tel: (852) 3129 2000 Fax: (852) 2856 2611

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5/25/2015

## GIOTRIF® (Boehringer Ingelheim)

Prepared by Fiona Yuen and edited by Ivy Chan

### Active Ingredient:

Afatinib (as dimaleate)

### Presentation:

Giotrif 20mg – Each film-coated tablet contains 20 mg of afatinib (as dimaleate);

Giotrif 30mg – Each film-coated tablet contains 30 mg of afatinib (as dimaleate);

Giotrif 40mg – Each film-coated tablet contains 40 mg of afatinib (as dimaleate).

### Pharmacological Properties:

Afatinib is a potent and selective, irreversible ErbB Family Blocker. Afatinib covalently binds to and irreversibly blocks signalling from all homo- and heterodimers formed by the ErbB family members EGFR (ErbB1), HER2 (ErbB2), ErbB3 and ErbB4.

In non-clinical disease models with ErbB pathway deregulation, afatinib as a single agent effectively blocks ErbB receptor signalling resulting in tumour growth inhibition or tumour regression. NSCLC tumours with common activating EGFR mutations (Del 19, L858R) and several less common EGFR mutations in exon 18 (G719X) and exon 21 (L861Q) are particularly sensitive to afatinib treatment in non-clinical and clinical settings.

Afatinib retains significant anti-tumour activity in NSCLC cell lines *in vitro* and/or tumour models *in vivo* (xenografts or transgenic models) driven by mutant EGFR isoforms known to be resistant to the reversible EGFR inhibitors erlotinib and gefitinib such as T790M or T854A. Clinically, activity in tumours harbouring the T790M mutation in exon 20 has also been shown. Limited non clinical and/or clinical activity was observed in NSCLC tumours with insertion mutations in exon 20.

### Indications:

GIOTRIF as monotherapy is indicated for the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).

### Dosage & Administration:

Treatment with GIOTRIF should be initiated and supervised by a physician experienced in the use of anticancer therapies.

EGFR mutation status should be established prior to initiation of GIOTRIF therapy.

### Posology

The recommended dose is 40 mg once daily.

This medicinal product should be taken without food. Food should not be consumed for at least 3 hours before and at least 1 hour after taking this medicinal product.

GIOTRIF treatment should be continued until disease progression or until no longer tolerated by the patient (see Table 1 below).

### Dose adjustment for adverse reactions

Symptomatic adverse reactions (e.g. severe/persistent diarrhoea or skin related adverse reactions) may be successfully managed by treatment interruption and dose reductions or treatment discontinuation of GIOTRIF as outlined in Table 1.

Table 1. Dose adjustment information for adverse reactions

| CTCAE <sup>a</sup> Adverse reactions                         | Recommended dosing                     |   |
|--|--|---|
| Grade 1 or Grade 2   | No interruption <sup>b</sup>           | No dose adjustment  |
| Grade 2 (prolonged <sup>c</sup> or intolerable) or Grade ≥ 3 | Interrupt until Grade 0/1 <sup>b</sup> | Resume with dose reduction by 10 mg decrements <sup>d</sup> |

<sup>a</sup> NCI Common Terminology Criteria for Adverse Events

<sup>b</sup> In case of diarrhoea, anti-diarrhoeal medicinal products (e.g. loperamide) should be taken immediately and continued for persistent diarrhoea until loose bowel movements cease.

<sup>c</sup> > 48 hours of diarrhoea and/or > 7 days of rash

<sup>d</sup> If patient cannot tolerate 20 mg/day, permanent discontinuation of GIOTRIF should be considered

Interstitial Lung Disease (ILD) should be considered if a patient develops acute or worsening of respiratory symptoms in which case treatment should be interrupted pending evaluation. If ILD is diagnosed, GIOTRIF should be discontinued and appropriate treatment initiated as necessary.

### Missed dose

If a dose is missed, it should be taken within the same day as soon as the patient remembers. However, if the next scheduled dose is due within 8 hours then the missed dose must be skipped.

### Use of P-glycoprotein (P-gp) inhibitors

If P-gp inhibitors need to be taken, they should be administered using staggered dosing, i.e. the P-gp inhibitor dose should be taken as far apart in time as possible from the GIOTRIF dose. This means preferably 6 hours (for P-gp inhibitors dosed twice daily) or 12 hours (for P-gp inhibitors dosed once daily) apart from GIOTRIF.

### Patients with renal impairment

The safety, pharmacokinetics and efficacy of this medicinal product have not been studied in a dedicated trial in patients with renal impairment. Adjustments to the starting dose are not necessary in patients with mild or moderate renal impairment. Treatment in patients with severely impaired renal function (< 30 mL/min creatinine clearance) is not recommended.

### Patients with hepatic impairment

Exposure to afatinib is not significantly changed in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Adjustments to the starting dose are not necessary in patients with mild or moderate hepatic impairment. This medicinal product has not been studied in patients with severe (Child Pugh C) hepatic impairment. Treatment in this population is not recommended.

### Paediatric population

There is no relevant use of GIOTRIF in the paediatric population in the indication of NSCLC. Therefore, treatment of children or adolescents with this medicinal product is not recommended.

### Method of administration

This medicinal product is for oral use. The tablets should be swallowed whole with water. If swallowing of whole tablets is not possible, these can be dispersed in approximately 100 ml of noncarbonated drinking water. No other liquids should be used. The tablet should be dropped into the water without crushing it, and stirred occasionally for up to 15 min until it is broken up into very small particles. The dispersion should be consumed immediately. The glass should be rinsed with approximately 100 ml of water which should also be consumed. The dispersion can also be administered through a gastric tube.

### Contraindications:

Hypersensitivity to afatinib or to any of the excipients

## **Precautions:**

### Assessment of EGFR mutation status

When assessing the EGFR mutation status of a patient, it is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations.

### Diarrhoea

Diarrhoea, including severe diarrhoea, has been reported during treatment with GIOTRIF. Diarrhoea may result in dehydration with or without renal impairment, which in rare cases has resulted in fatal outcomes. Diarrhoea usually occurred within the first 2 weeks of treatment. Grade 3 diarrhoea most frequently occurred within the first 6 weeks of treatment.

Proactive management of diarrhoea including adequate hydration combined with anti-diarrhoeal medicinal products especially within the first 6 weeks of the treatment is important and should start at first signs of diarrhoea. Antidiarrhoeal medicinal products (e.g. loperamide) should be used and if necessary their dose should be escalated to the highest recommended approved dose. Anti-diarrhoeal medicinal products should be readily available to the patients so that treatment can be initiated at first signs of diarrhoea and continued until loose bowel movements cease for 12 hours. Patients with severe diarrhoea may require interruption and dose reduction or discontinuation of therapy with GIOTRIF. Patients who become dehydrated may require administration of intravenous electrolytes and fluids.

### Skin related adverse events

Rash/acne has been reported in patients treated with this medicinal product. In general, rash manifests as a mild or moderate erythematous and acneiform rash, which may occur or worsen in areas exposed to sun. For patients who are exposed to sun, protective clothing, and use of sun screen is advisable. Early intervention (such as emollients, antibiotics) of dermatologic reactions can facilitate continuous GIOTRIF treatment. Patients with severe skin reactions may also require temporary interruption of therapy, dose reduction, additional therapeutic intervention, and referral to a specialist with expertise in managing these dermatologic effects.

Bullous, blistering and exfoliative skin conditions have been reported including rare cases suggestive of Stevens-Johnson syndrome. Treatment with this medicinal product should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

### Female gender, lower body weight, and underlying renal impairment

Higher exposure to afatinib has been observed in female patients, patients with lower body weight and those with underlying renal impairment. This could result in a higher risk of developing adverse reactions in particular diarrhoea, rash/acne and stomatitis. Closer monitoring is recommended in patients with these risk factors.

### Interstitial Lung Disease (ILD)

There have been reports of ILD or ILD-like adverse reactions (such as lung infiltration, pneumonitis, acute respiratory distress syndrome, allergic alveolitis), including fatalities, in patients receiving GIOTRIF for treatment of NSCLC. ILD-like adverse reactions were reported in 0.7% of more than 3,800 patients treated. CTCAE Grade  $\geq 3$  ILD-like adverse reactions were reported in 0.5% of patients. Patients with a history of ILD have not been studied.

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude ILD. Treatment with this medicinal product should be interrupted pending investigation of these symptoms. If ILD is diagnosed, GIOTRIF should be

permanently discontinued and appropriate treatment initiated as necessary.

### Severe hepatic impairment

Hepatic failure, including fatalities, has been reported during treatment with this medicinal product in less than 1% of patients. In these patients, confounding factors have included pre-existing liver disease and/or comorbidities associated with progression of underlying malignancy. Periodic liver function testing is recommended in patients with pre-existing liver disease. Grade 3 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations were observed in 2.4% of patients with normal baseline liver tests treated with 40 mg/day, and were about 3.5 fold higher in patients with abnormal baseline liver tests. Dose interruption may become necessary in patients who experience worsening of liver function. In patients who develop severe hepatic impairment while taking GIOTRIF, treatment should be discontinued.

### Keratitis

Symptoms such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. This medicinal product should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.

### Left ventricular function

Left ventricular dysfunction has been associated with HER2 inhibition. Based on the available clinical trial data, there is no suggestion that this medicinal product causes an adverse reaction on cardiac contractility. However, this medicinal product has not been studied in patients with abnormal left ventricular ejection fraction (LVEF) or those with significant cardiac history. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

In patients with an ejection fraction below the institution's lower limit of normal, cardiac consultation as well as treatment interruption or discontinuation should be considered.

### P-glycoprotein (P-gp) interactions

Concomitant treatment with strong inducers of P-gp may decrease exposure to afatinib.

### Lactose

This medicinal product contains lactose. Patients with rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

## **Drug Interactions:**

### Interactions with drug transport systems

#### *Effects of P-gp and breast cancer resistance protein (BCRP) inhibitors on afatinib*

*In vitro* studies have demonstrated that afatinib is a substrate of P-gp and BCRP. When the strong P-gp and BCRP inhibitor ritonavir (200 mg twice a day for 3 days) was administered 1 hour before a single dose of 20 mg GIOTRIF, exposure to afatinib increased by 48% (area under the curve (AUC<sub>0-∞</sub>)) and 39% (maximum plasma concentration (C<sub>max</sub>)). In contrast, when ritonavir was administered simultaneously or 6 hours after 40 mg GIOTRIF, the

relative bioavailability of afatinib was 119% (AUC<sub>0-∞</sub>) and 104% (C<sub>max</sub>) and 111% (AUC<sub>0-∞</sub>) and 105% (C<sub>max</sub>), respectively. Therefore, it is recommended to administer strong P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) using staggered dosing, preferably 6 hours or 12 hours apart from GIOTRIF.

#### Effects of P-gp inducers on afatinib

Pre-treatment with rifampicin (600 mg once daily for 7 days), a potent inducer of P-gp, decreased the plasma exposure to afatinib by 34% (AUC<sub>0-∞</sub>) and 22% (C<sub>max</sub>) after administration of a single dose of 40 mg GIOTRIF. Strong P-gp inducers (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital or St. John's wort (*Hypericum perforatum*)) may decrease exposure to afatinib.

#### Effects of afatinib on P-gp substrates

Based on *in vitro* data, afatinib is a moderate inhibitor of P-gp. However, based on clinical data it is considered unlikely that GIOTRIF treatment will result in changes of the plasma concentrations of other P-gp substrates.

#### Interactions with BCRP

*In vitro* studies indicated that afatinib is a substrate and an inhibitor of the transporter BCRP. Afatinib may increase the bioavailability of orally administered BCRP substrates (including but not limited to rosuvastatin and sulfasalazine).

#### Food effect on afatinib

Co-administration of a high-fat meal with GIOTRIF resulted in a significant decrease of exposure to afatinib by about 50% in regard to C<sub>max</sub> and 39% in regard to AUC<sub>0-∞</sub>. This medicinal product should be administered without food.

#### Side Effects:

##### Summary of the safety profile

The types of adverse reactions (ADRs) were generally associated with the EGFR inhibitory mode of action of afatinib. The summary of all ADRs is shown in Table 2. The most frequent ADRs were diarrhoea and skin related adverse events as well as stomatitis and paronychia (see also Table 3). ILD-like adverse reactions were reported in 0.7% of afatinib treated patients. Overall, dose reduction led to a lower frequency of common adverse reactions.

In patients treated with once daily GIOTRIF 40 mg, dose reductions due to ADRs occurred in 57% of the patients. Discontinuation due to ADRs diarrhoea and rash/acne was 1.3% and 0%, respectively.

Bullous, blistering and exfoliative skin conditions have been reported including rare cases suggestive of Stevens-Johnson syndrome although in these cases there were potential alternative aetiologies.

#### Tabulated list of adverse reactions

Table 2 summarises the frequencies of ADRs pooled from all NSCLC trials with daily GIOTRIF doses of 40 mg (N=497) or 50 mg (N=1638) as monotherapy. The following terms are used to rank the ADRs by frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

#### Description of selected adverse reactions

Very common ADRs in GIOTRIF-treated patients occurring in at least 10% of patients in trial LUX-Lung 3 are summarised by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Table 3.

| Body System  | Very common (≥1/10)  | Common (≥1/100 to <1/10)   | Uncommon (≥1/1,000 to <1/100) |
|--|--|--|-------------------------------|
| Infections and infestations                          | Paronychia <sup>1</sup>  | Cystitis   |                               |
| Metabolism and nutrition disorders                   | Decreased appetite   | Dehydration<br>Hypokalaemia  |                               |
| Nervous system disorders                             |  | Dysgeusia  |                               |
| Eye disorders  |  | Conjunctivitis<br>Dry eye  | Keratitis                     |
| Respiratory, thoracic and mediastinal disorders      | Epistaxis  | Rhinorrhoea  | Interstitial lung disease     |
| Gastrointestinal disorders                           | Diarrhoea<br>Stomatitis <sup>2</sup>   | Dyspepsia<br>Cheilitis   |                               |
| Hepatobiliary disorders                              |  | Alanine aminotransferase increased<br>Aspartate aminotransferase increased |                               |
| Skin and subcutaneous tissue disorders               | Rash <sup>3</sup><br>Dermatitis acneiform <sup>4</sup><br>Pruritus <sup>5</sup><br>Dry skin <sup>6</sup> | Palmar-plantar erythrodysesthesia syndrome                                 |                               |
| Musculoskeletal and connective tissue disorders      |  | Muscle spasms  |                               |
| Renal and urinary disorders                          |  | Renal impairment/<br>Renal failure   |                               |
| General disorders and administration site conditions |  | Pyrexia  |                               |
| Investigations                                       |  | Weight decreased   |                               |

<sup>1</sup> Includes Paronychia, Nail infection, Nail bed infection

<sup>2</sup> Includes Stomatitis, Aphthous stomatitis, Mucosal inflammation, Mouth ulceration, Oral mucosa erosion, Mucosal erosion, Mucosal ulceration

<sup>3</sup> Includes group of rash preferred terms

<sup>4</sup> Includes Acne, Acne pustular, Dermatitis acneiform

<sup>5</sup> Includes Pruritus, Pruritus generalised

<sup>6</sup> Includes Dry skin, Skin chapped

|  | GIOTRIF (40 mg/day) N=229 |      |     | Pemetrexed/ Cisplatin N=111 |     |   |
|--|---------------------------|------|-----|-----------------------------|-----|---|
|  | Any Grade                 | 3    | 4   | Any Grade                   | 3   | 4 |
| MedDRA Preferred Term                                  | %                         | %    | %   | %                           | %   | % |
| <i>Infections and infestations</i>                     |                           |      |     |                             |     |   |
| Paronychia <sup>1</sup>                                | 57.6                      | 11.4 | 0   | 0                           | 0   | 0 |
| <i>Metabolism and nutrition disorders</i>              |                           |      |     |                             |     |   |
| Decreased appetite                                     | 20.5                      | 3.1  | 0   | 53.2                        | 2.7 | 0 |
| <i>Respiratory, thoracic and mediastinal disorders</i> |                           |      |     |                             |     |   |
| Epistaxis  | 13.1                      | 0    | 0   | 0.9                         | 0.9 | 0 |
| <i>Gastrointestinal disorders</i>                      |                           |      |     |                             |     |   |
| Diarrhoea  | 95.2                      | 14.4 | 0   | 15.3                        | 0   | 0 |
| Stomatitis <sup>2</sup>                                | 69.9                      | 8.3  | 0.4 | 13.5                        | 0.9 | 0 |
| Cheilitis  | 12.2                      | 0    | 0   | 0.9                         | 0   | 0 |
| <i>Skin and subcutaneous tissue disorders</i>          |                           |      |     |                             |     |   |
| Rash <sup>3</sup>                                      | 70.3                      | 14   | 0   | 6.3                         | 0   | 0 |
| Dermatitis acneiform <sup>4</sup>                      | 34.9                      | 2.6  | 0   | 0                           | 0   | 0 |
| Dry skin <sup>5</sup>                                  | 29.7                      | 0.4  | 0   | 1.8                         | 0   | 0 |
| Pruritus <sup>6</sup>                                  | 19.2                      | 0.4  | 0   | 0.9                         | 0   | 0 |
| <i>Investigations</i>                                  |                           |      |     |                             |     |   |
| Weight decreased                                       | 10.5                      | 0    | 0   | 9.0                         | 0   | 0 |

<sup>1</sup> Includes Paronychia, Nail infection, Nail bed infection

<sup>2</sup> Includes Stomatitis, Aphthous stomatitis, Mucosal inflammation, Mouth ulceration, Oral mucosa erosion, Mucosal erosion, Mucosal ulceration

<sup>3</sup> Includes group of rash preferred terms

<sup>4</sup> Includes Acne, Acne pustular, Dermatitis acneiform

<sup>5</sup> Includes Dry skin, Skin chapped

<sup>6</sup> Includes Pruritus, Pruritus generalised

#### Liver function test abnormalities

Liver function test abnormalities (including elevated ALT and AST) were observed in patients receiving GIOTRIF 40 mg. These elevations were mainly transient and did not lead to discontinuation. Grade 2 (> 2.5 to 5.0 times upper limit of normal (ULN)) ALT elevations occurred in < 8% of patients treated with this medicinal product. Grade 3 (> 5.0 to 20.0 times ULN) elevations occurred in <4% of patients treated with GIOTRIF.

#### Forensic Classification:

P1S1S3

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Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

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Ref: Prevenar 13<sup>®</sup> Pneumococcal polysaccharide conjugate vaccine (13-valent adsorbed) Prescribing Information. Pfizer Corporation Hong Kong Limited. Version July 2014  
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