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The Pharmaceutical Society of Hong Kong
The Practising Pharmacists Association of Hong Kong
The Society of Hospital Pharmacists of Hong Kong

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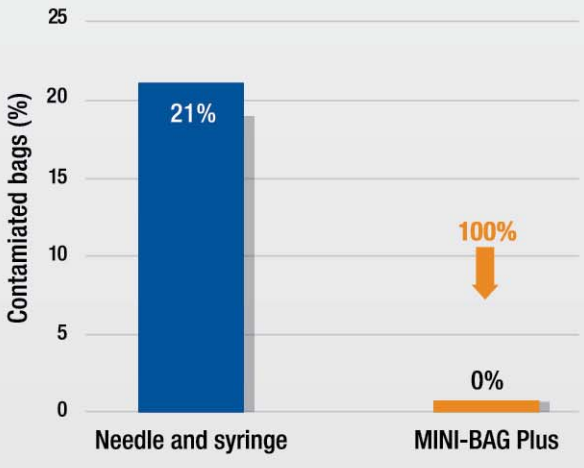
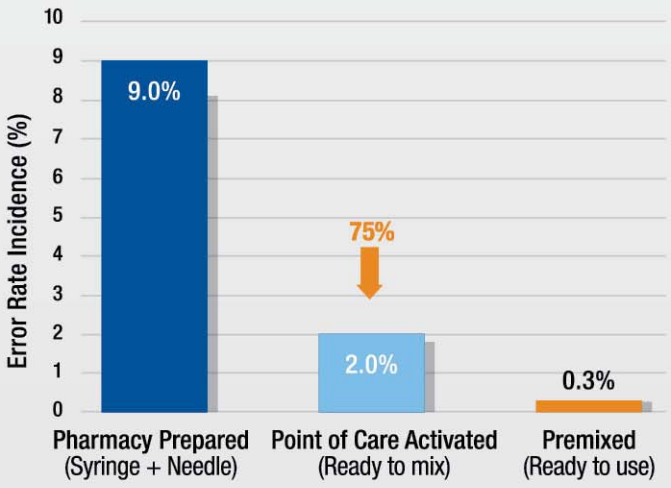


A point-of-care activated system can reduce the risk of medication errors



1 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
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3 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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Generic Drugs versus Biosimilars: How Much You Know?

Traditionally, the majority of agents used for the treatment of diseases are small molecular drugs (SMDs). Most of them are pure inorganic or organic compound which could be fully duplicated via chemical reactions or synthesis and sold as a generic drug in contrast to the branded drug. Generic drugs, in most instances, can be characterized by analytical techniques to demonstrate identical therapeutic effect via modification or regulation of the structure and function of endogenous biologic components, usually cell-surface receptors, intra-cellular signal transduction elements, or circulating proteins.

On the other hand, biologics are macromolecules. They used to play a less significant role in the treatment of diseases until three decades ago. Designed biologics have become more and more eminent due to the advancement of genetic engineering which has revolutionized the treatment of many metabolic and degenerative diseases such as anemia, diabetes, cancer, hepatitis, multiple sclerosis, rheumatoid arthritis, and inflammatory bowel diseases.

Today over 140 different designed biologics have been invented and approved for use in the United States, with many more in the pipeline.[1] These innovative biologics with their patents going to expire sooner or later are produced in living cells with a multi-step process via genetic manipulation of an organism, such as yeast, mammalian cell line or animal followed by extraction, purification and formulation.[2] Initially, a protein molecule is translated from a DNA sequence and then modified, including further alterations and additions called post-translational modifications. The impact of post-translational modifications on a biologics is similar to the impact of a farm environment on the quality of grape. The appearance and taste of the same type of grape could vary in different growth conditions because of the soil, the nutrient and the weather elements such as sunlight, temperature and rain. Similarly, even the same biological system is used, designed biologics may have different types and degree of modifications, which in turn affect the quality, safety or effectiveness of the product.[3]

Although generic drug is identical to a small molecule reference medicine, similar biologics cannot and are not required to be exactly like their reference product as long as there is no clinically meaningful differences between the two products in term of their quality, safety and potency. Due to the greater size and complexity of biologics and the heterogeneity of biological processes, current science does not allow one to make “identical” copies of a biologic or even to analyze them to the level of precision that is possible for SMDs that are the same as their reference listed drug. In fact, as analytical techniques improve, more and more differences at the molecular level are seen between similar biologics produced by different manufacturers. So for the foreseeable future, biosimilars will remain “similar”, and not the “same”, as their reference products. This is basically how the idea of biosimilar evolved.

It is no doubt that biosimilars present more challenges than conventional generics in many aspects. For example, producer has to submit detail information such as production process and characterization, data of their stability and structure, potential cause of allergy to some people and requirement of large clinical trials, etc for validation before seeking approval for their clinical use. In this aspect, biosimilars are essentially newly manufactured versions of formerly patent protected biologics that will be marketed by competing developers as the development cost of biosimilars normally is around one tenth to one fourth of that for their innovative reference medicine and takes about 7 to 8 years’ effort to complete the whole product development. In contrast the developmental cost and time for a generic drug is about US$2-3M and 2-3 years, respectively.

Similar to any drug development in these days, pharmacovigilance is also an important issue for biosimilar drugs because these are not reference medicine as such, and are from different manufacturer from the reference products. Many adverse effects may appear only after a biosimilar drug is used more extensively, for a longer period of time, in a greater number of patients. Both manufacturers and prescriber should be aware of the importance of post marketing vigilance, and careful on patients taking biosimilar.

Amongst all countries, the European Community is probably the first to consider sale of biosimilars for treatment of diseases. In 2004, a legal basis and regulatory guidance for the development of biosimilar was introduced by the European Medicines Agency. Since then the guidance has flourished and been evolved to secure high standard biosimilar pharmaceuticals for patients’ use throughout the European Union. On the other hand, the acceptance of biosimilars in the United States took a longer path as biologics and SMDs are regulated under two separate statutes, i.e. the Public Health Services Act (PHSA) 351 and the Food, Drug and Cosmetic Act (FDCA) 505, respectively. On top of this, the underlying science for biologics is also in some ways more complex than for SMDs. This explains why the EU is years ahead of the US, having its first biosimilar approved in 2006 with over a dozen biosimilar filing approved since then in EU.

According to Rader’s study, it was found that most biosimilar companies and products in development are carried out in Asia and the Pacific Rim followed by the U.S. and EU. Interestingly, there are about 100 biopharmaceutical companies actively involved in research and development, manufacturing and marketing of biosimilar therapeutic products in India. There were 14 therapeutic drugs (similar biologics) available in 50 brands in 2005; the number has significantly increased to 20 therapeutic drugs in 250 brands in 2011. Biosimilar therapeutic products include insulin, erthropoietin, chorionic gonadotropin, streptokinase, interferon and heparin. It is concluded that the growing biosimilars market offers huge potential for companies involved in manufacturing, research and development.[4]

Hon-Yeung Cheung
Editor-in-Chief
October 30, 2015

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Haemorrhagic Risks of Antidepressants and NSAID Concomitant Use

Date: June 16, 2015

Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitor (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and monoamine oxidase inhibitors (MAOIs) are major classes of antidepressants in use, which are effective in alleviating depression. However, the concern of antidepressants causing abnormal bleeding lingers. Similar concern exists for non-steroidal anti-inflammatory drugs (NSAIDs) as well. The reason for these concerns is that previous studies found the association of upper gastrointestinal haemorrhage with the use of SSRIs, NSAIDs or combination of both.

As little is known about the risk of intracranial haemorrhage associated with separate and concurrent use of antidepressants and NSAIDs, this study was carried out between January 2009 and December 2013. The Korean Health Insurance Review and Assessment Service Database was used for collecting data related to drug prescription, health care usage and basic information like age and sex. 5,168,833 Korean patients without prior antidepressant prescription were selected for this cohort study. The rates of diagnosis of intracranial haemorrhage within 30 days were compared between two equally sized groups (antidepressant plus NSAIDs and antidepressant alone).

After the investigation, patients with simultaneous use of antidepressant and NSAID were more prone to intracranial haemorrhage than counterpart with antidepressant usage alone. This suggests that there is a significant drug interaction between the two in causing intracranial bleeding. Furthermore, classes of antidepressant have shown similar risk of the haemorrhage. Other factors such as age, subtype of intracranial haemorrhage, co-medications and co-morbidities are not associated with intracranial bleeding.

Nevertheless, this study has not investigated the association between antidepressant prescription and intracranial haemorrhage. Therefore, the hypothesis of the drug alone causing intracranial haemorrhage by blocking platelet uptake cannot be confirmed. As antidepressant can elevate the concentration of epinephrine which is associated with intracranial haemorrhage, it is likely to be the cause of the problem alone but further study is required.

In conclusion, it is recommended to closely monitor patients for intracranial haemorrhage if they have concurrent use of antidepressants and NSAIDs.

Source: www.bmj.com

Sitagliptin Does Not Compromise Cardiovascular Outcomes

Date: July 16, 2015

The long term effect of sitagliptin, a dipeptidyl peptidase 4 inhibitor, on cardiovascular events has been uncertain. A research was carried out to study the long-term effect of adding sitagliptin to usual care in patients with type 2 diabetes on cardiovascular diseases.

In this randomized, double-blind study, 14,671 patients were assigned to add either sitagliptin or placebo to their existing therapy. Open-label use of antihyperglycemic therapy was encouraged as required, and reaching individually appropriate glycemic targets was aimed in all patients. To determine whether sitagliptin was noninferior to placebo, a relative risk of 1.3 was used as the marginal upper boundary. The primary cardiovascular outcome was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina.

Overall, the primary outcome occurred in 839 patients in the sitagliptin group (11.4%; 4.06 per 100 person-years) and 851 patients in the placebo group (11.6%; 4.17 per 100 person-years). Sitagliptin was noninferior to placebo for the primary composite cardiovascular outcome (hazard ratio, 0.98; 95% CI, 0.88 to 1.09; P<0.001). Rates of hospitalization for heart failure did not differ between the two groups (hazard ratio, 1.00; 95% CI, 0.83 to 1.20; P=0.98). There were no significant between-group differences in rates of acute pancreatitis (P=0.07) or pancreatic cancer (P=0.32).

In conclusion, among patients with type 2 diabetes and established cardiovascular diseases, adding sitagliptin to usual care was not associated with an increased risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse events.

Source: www.nejm.org

Anti-inflammatory Roles of Colchicine in Acute Coronary Syndrome

Date: August 24, 2015

Colchicine, a common drug used in acute gout and other inflammatory conditions, has been found to inhibit local cardiac production of three inflammatory cytokines – interleukin (IL)-1β, IL-18, and downstream IL-6 – in patients with acute coronary syndrome (ACS).

The study was conducted from 2013 to 2014 in Australia. 40 ACS patients, 33 patients with stable coronary artery disease (CAD), and 10 patients with no angiographically significant CAD, were included. ACD and stable CAD patients were randomly assigned to receive oral colchicine treatment (1mg followed by 0.5mg one hour later) or no colchicine treatment, 6 to 24 hours before cardiac catheterization. IL-1β, IL-18, and IL-6 levels in blood collected from the coronary sinus (CS), aortic root, and lower right atrium of patients were tested.

The transcoronary (coronary sinus-arterial) gradients for IL-1β, IL-18, and IL-6 were highest in ACS patients and lowest in patients without obstructive CAD, thus all three inflammatory cytokines studied were highly associated with disease activity. Moreover, in ACS patients, the levels of IL-1b, IL-18, and IL-6 were significantly higher

in the coronary sinus than in the aortic root and lower right atrium. This implied venous plasma concentrations of these cytokines could not help reliably identify an increase in transcoronary production.

Colchicine administration in ACS patients significantly reduced the transcoronary gradients of all three cytokines. The exact mechanisms by which colchicine inhibits the production of these inflammatory cytokines were not deeply investigated in this research, though other studies have shown that colchicine might suppress nucleotide-binding oligomerization domain-like receptors, pyrin domain-containing 3 (NLRP3) inflammasome, which promotes the production of these cytokines.

Colchicine, as an oral, inexpensive, and potent anti-inflammatory drug, could induce acute inhibition of some key inflammatory cytokines in widespread vascular inflammation of ACS, thus reduces the incidence of new coronary events by stabilizing culprit and non-culprit lesions.

Source: jaha.ahajournals.org

Initiating Treatment with Combination Therapy in Pulmonary Hypertension

Date: August 27, 2015

A research was conducted to study the effect of initial combination therapy with ambrisentan and tadalafil on the long-term outcomes in patients with pulmonary arterial hypertension. Current relevant data are scarce.

In this event-driven, double-blind study, patients with World Health Organization functional class II or III symptoms of pulmonary arterial hypertension and had not previously received treatment were included. In a 2:1:1 ratio, the participants were randomly assigned to receive an initial combination therapy with 10 mg of ambrisentan plus 40 mg of tadalafil (combination-therapy group), 10 mg of ambrisentan plus placebo (ambrisentan-monotherapy group), or 40 mg of tadalafil plus placebo (tadalafil-monotherapy group), all administered once daily. The primary end point in a time-to-event analysis was the first event of clinical failure, which was defined as the first occurrence of a composite of death, hospitalization for worsening pulmonary arterial hypertension, disease progression, or unsatisfactory long-term clinical response.

The primary analysis included 500 participants; 253 were assigned to the combination-therapy group, 126 to the ambrisentan-monotherapy group, and 121 to the tadalafil-monotherapy group. A primary end-point event occurred in 18%, 34%, and 28% of the participants in these groups respectively, and in 31% of the pooled-monotherapy group (the two monotherapy groups combined). Adverse events including peripheral edema, headache, nasal congestion, and anemia, occurred more frequently in the combination-therapy group than in either monotherapy group.

All in all, among participants with pulmonary arterial hypertension who had not received previous treatment, initial combination therapy with ambrisentan and tadalafil resulted in a significantly lower risk of clinical-failure events than that with ambrisentan or tadalafil monotherapy.

Source: www.nejm.org

DPP-4 inhibitors May Cause Severe Joint Pain, FDA warns

Date: August 28, 2015

The U.S. Food and Drug Administration (FDA) issued a warning about the joint pain caused by type 2 diabetes medicines sitagliptin, saxagliptin, linagliptin and alogliptin. Such joint pain can be severe and disabling. A new Warning and Precaution about this risk has been added to the labels of all dipeptidyl peptidase-4 (DPP-4) inhibitors.

DPP-4 inhibitors are used along with diet and exercise to reduce blood sugar level in adults with type 2 diabetes. Untreated type 2 diabetes can lead to serious problems, including blindness and heart disease.

Cases of severe joint pain in relation to the use of DPP-4 inhibitors were identified with the search of FDA Adverse Event Reporting System database and other medical literature. Symptoms appeared from 1 day to years after the patients started taking a DPP-4 inhibitor. These symptoms were relieved when the patients discontinued the medication, usually in less than a month.

Patients are advised to contact their healthcare professional right away if they experience severe and persistent joint pain, instead of stop taking their DPP-4 inhibitor. In addition, healthcare professionals should consider DPP-4 inhibitors as a possible cause of severe joint pain and discontinue the drug if appropriate.

Source: www.fda.gov

Spironolactone – Drug of Choice in Resistant Hypertension

Date: August 31, 2015

It was noted that from European Society of Cardiology (ESC) on 31 August 2015 that in patients with resistant hypertension despite the treatment of 3 drugs, adding spironolactone and a diuretic, can be significantly more effective than adding other blood pressure (BP) lowering drugs, according to the trial results of PATHWAY-2.

The PATHWAY 2 examined the extent of lowering BP among different drugs, including spironolactone, and two other anti-hypertensives which have different mechanisms of action: doxazosin for reducing arterial resistance, and bisoprolol for reducing cardiac output.

The target group were patients with resistant hypertension who were already treated with maximum tolerable doses of a combination of three drugs - an ACE-inhibitor or angiotensin receptor blocker (ARB); a calcium channel blocker (CCB); and a thiazide type diuretic. In addition to these, patients were randomised to sequentially receive 12 weeks of spironolactone (25-50 mg), bisoprolol (5-10 mg), doxazosin (4-8 mg modified release) and placebo in random order. BP was measured and recorded both in the clinic and at home over 4 consecutive days at baseline as well as at 6 and 12 weeks of each treatment cycle. Among 314 patients, spironolactone has the

best home systolic blood pressure control (a reduction of 8.70 mmHg, P<0.001) compared to placebo; doxazosin (a reduction of 4.03 mmHg, P<0.001), and bisoprolol (a reduction of 4.48 mmHg, P<0.001).

From this study, it is clear that compared to bisoprolol or doxazosin, spironolactone, which promotes sodium excretion, is probably the most effective drug in treating resistant hypertension.

Source: www.escardio.org

Oral Influenza Vaccine Is Possible, Preliminary Results Show

Date: September 1, 2015

Vaccine against influenza A H1N1 is being expected to be formulated as a tablet, with initial test results showing that it is seemingly safe and effective.

The vaccine is based on an adenovirus type 5 vector modified to remove genes needed for replication, with an added gene that expresses a small double-stranded RNA hairpin molecule, as a built-in adjuvant. After immunization, 11 (92%) of 12 vaccine-treated participants had a four-fold increase in haemagglutination inhibition titres and microneutralization titres. Individuals who were given a tablet containing the adenovirus type 5 H1 vaccine were found to have favourable tolerance to it and neutralizing antibody responses to influenza virus were elicited.

Apparently, orally administered tablet predominates over traditional vaccine. It simplifies shipment, storage, administration and eliminates sterilization. Efficient manufacture of influenza has become increasingly important, when changes in seasonal influenza are becoming more frequent, leading to possible outbreak of pandemic in no time. Using cell culture rather than specific pathogen-free eggs enables rapid manufacture of influenza vaccine to meet its growing demand. Cheap and speedy mass production of this vaccine remains to be shown. Furthermore, oral vaccines could be sent through the postal system to individuals, avoiding the assembly required for vaccination, hence reducing risks of human-to-human transmission of infectious diseases.

Promising as this study may seem, uncertainties do exist. The viral vector might cause diseases and previous immunity to the vector might interfere with immune responses to the inserted gene (influenza). The vaccine is still under cautious investigation before it can be officially launched.

Source: www.thelancet.com

Protease Inhibitor Monotherapy: an Alternative for Long-term Management of HIV

Date: September 15, 2015

Existing HIV treatment guidelines recommend the use of a combination of drugs in antiretroviral therapy. A recent study has shown that protease inhibitor monotherapy could be an alternative for long-term clinical management of HIV infection.

The parallel-group, open-label, non-inferiority trial was conducted in the UK. Between 2008 and 2010, 587 adults positive for HIV with suppressed viral load were randomly allocated to maintain ongoing triple therapy (OT) (291 participants) or switch to a physician-selected ritonavir-boosted protease inhibitor monotherapy (PI-mono) (296 participants). The followed-up period lasted for 3 to 5 years.

After 3 years, loss of drug options was observed in two participants (Kaplan-Meier estimate 0.7%) in the OT group and six (2.1%) in the PI-mono group, with a difference of 1.4% (–0.4 to 3.4). This finding indicated the non-inferiority of protease inhibitor monotherapy, when compared to continuous combination treatment, in the preservation of future treatment options.

However, high levels of viral load rebound were found in the PI-mono group. There were one or more episodes of confirmed viral load rebound in eight patients (Kaplan-Meier estimate 3.2%) in the OT group and ninety-five (35.0%) in the PI-mono group. When the combination treatment was promptly reintroduced, all patients with viral load rebound in the PI-mono group achieved full viral load suppression.

Protease inhibitor monotherapy, with regular viral load monitoring, could be a suitable alternative for HIV patients who are stable on treatment and wish to reduce their exposure to specific drugs or multiple drug classes.

Source: www.thelancet.com

Digoxin Treatment: Benefits Still Outweigh Risks

Date: September 15, 2015

Digitalis have been widely used in heart failure and atrial fibrillation. Recently, observational studies reported increased mortality with digoxin. The safety concern has led to a decline in its use. In view of the potential efficacy of digoxin in heart failure and atrial fibrillation management, and in an attempt to settle the uncertainty over adverse outcomes, the efficacy and safety of digoxin in all available observational and experimental studies were assessed in a meta-analysis.

All studies that compared outcomes in digoxin treatment and control (placebo or no treatment) groups, regardless of the study design, were evaluated. All cardiovascular outcomes and all populations were included. Studies were excluded if they did not provide comparative outcomes, or were not published as full text articles in English. 52 studies were identified for systematic review, including 621 845 patients allocated to either digoxin treatment or control group, representing 2 248 775 patient years of follow-up.

The research found digoxin use had a neutral effect on mortality in randomised trials, and was associated with reduced hospital admissions. The association between digoxin and adverse outcomes in observational studies is likely to be non-causative, and a result of confounding factors that could not be statistically adjusted. More randomised trials on digoxin use are required to identify its place in the management of heart failure and atrial fibrillation.

Source: www.bmj.com

A Glimpse of Community Pharmacy in England

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ABSTRACT

Community pharmacies in England have a long history of serving the local population for their medication needs. Currently, the pharmacist services provided are differentiated into three levels: essential, advanced and enhanced. Apart from stream-lining the essential dispensing services, advanced services including Medicine Use Review and New Medicine Service are provided to improve the medication adherence for specific groups of patients. The system is optimized with enhanced services to meet specific needs of local area. Such a development carries some lessons for worldwide pharmacies to learn, especially for countries aiming at expanding the role of community pharmacists in public health.

Keywords: *Community pharmacy, advanced service, manage long-term medications, expanding roles of pharmacists, England, Hong Kong*

INTRODUCTION

In early 1900s, the practice of community pharmacists in the England had long been a ready source of advice on all sorts of subjects which was unpaid and informal, apart from making, selling and occasional dispensing of medications.[1] The founding of National Health Services (NHS) in 1948 significantly diminished their traditional advisory role due to the heavy workload from making up each prescription individually and dispensing.[2] Since the implementation of 1968 Medicines Act, pharmaceutical products have been defined under three legal categories: general sales list medicines (GSL), pharmacy medicines (P), and prescription only medicines (POM). Most medications had to be supplied or sold at a pharmacy under the supervision of pharmacists, except some pre-packed GSL can be sold at other premises such as supermarkets.[3]

In late 1970s, with increasing use of ready-to-use drugs and Vaughan intervention that suggested community pharmacies were dying, the professions had to reinvent themselves to have wider contribution in public health.[1] There were a number of pharmacy initiatives aimed at raising public awareness and expanding roles for pharmacists to promote health since then. WHO (1994) identified the role of community pharmacists in healthcare system.[4] Accumulated evidence suggested the benefits of pharmacist interventions.[5-7] Various papers published by the UK government purposed more roles for community pharmacists to improve public health.[8-11] Now community pharmacies remain an essential component of healthcare system in England, with estimated 11,500 community pharmacies serving 1.6 million people every day.[12]

SERVICES PROVIDED BY NHS CONTRACTED PHARMACY

The NHS contracted community pharmacy should provide essential services, advanced services and enhanced services under specifications.[12] Each community pharmacy can reimburse the corresponding dispensing items or services provided with reference to the drug tariff. Commissioners of the services include NHS England, Clinical Commissioning Group (CCGs) and Local Authorities.[13]

Essential services

Dispensing is the core part of the essential services. The latest statistics show that community pharmacies in England dispensed almost 1 billion prescription items in the year 2014, with more than 50% increase in the last 10 years.[14] Measures including electronic prescribing system (EPS) and pharmacy technicians have begun to be implemented to enhance the safe supply of medicines and appliances ordered on NHS prescriptions.

EPS currently accounts for 25% of overall prescriptions in England. It enables prescribers including general practitioners (GPs) to send electronic prescriptions efficiently to a dispenser in a pharmacy according to patients' preference. This helps the taking in and issuing of prescriptions, where the subsequent reviews bring convenience to staff and patients.[15] For an experienced technician with recognized training and education, they can take on more responsibilities as enhanced specialists such as accuracy checking technicians. They can give support on accuracy check of dispensed items to streamline the process of supplying medications. They can also carry administration work for stock ordering and putting stock away, and the payment of prescriptions for endorsing and filling prescriptions.[16-18]

These measurements can save more time for pharmacists to counsel patients on their prescriptions and resolve queries related to prescriptions. With appropriate information and advice provided, patients are enabled to utilize, store and dispose them safely and effectively. Records are kept for all medicines dispensed, any significant advices provided, referrals and interventions made. This allows pharmacists to manage repeat medications for up to one year, in partnership with patients and prescribers. The patients can return to the pharmacy for repeat supplies, without first having to visit the GP surgery.[16]

Apart from dispensing services, contracted pharmacies are also legally obligated to provide services of disposal of unwanted medicine; promotion of public health such as smoking cessation and flu vaccination campaigns; support for self-care of patients with self-limiting illness and long-term conditions;

signposting patients to other healthcare professionals when appropriate; and clinical governance to support excellent care.[12,17]

Advanced services

Four advanced services are currently funded by the NHS England, namely Medicine Use Reviews (MUR) and New Medicine Services (NMS), Appliance Use Review (AUR) and Stoma Application Customization (SAC).[19] Community pharmacies can choose to provide any of these services considering that they follow the requirements set by NHS. MUR and NMS are major drug optimization services to help eligible patients get the most out of their prescribed medications.

Medicine Use Review

MUR is a medicine check-up service usually provided in a private consultation area in the pharmacy. Patients can ask about their medications, where pharmacists will in turn provide more drug information such as side effects and identify potential drug-related problems. As worrying about side-effects is one of the causes of non-adherence, MUR will help reassure patients that some common side effects can often wear off encourage them continue the regime. Patients will go away better informed and more likely get the most out of their medications.[19-21]

MUR is provided by over 90% of community pharmacies in UK. Over 3 million MURs been conducted in England in financial year 2014-15.[22] As of 2015, community pharmacists are required to provide at least 70% of their MUR to one of the four target groups of patients: (a) patients taking high risk medications including anticoagulants and diuretics, (b) patients recently being discharged from hospitals who had changes made to their medicines while at hospitals, (c) patients with respiratory diseases; and (d) patients at risk of or diagnosed with cardiovascular/cardiovascular-risk condition with prescribed drug for treatment and taking at least four drugs overall.[23] From a qualitative study conducted by Latif and colleagues (2011), although some patients felt reassured about their medicines, they identified the needs of improvement of pharmacist consultation skills for implementing the MUR service more effectively.[24] PSNC updated a list of questions to help shape the MUR consultation **(Table 1)**. More updated evidence will be published to assess the effectiveness of MUR.[25]

Table 1. Examples of guideline questions in MUR service (Adopted from Pharmaceutical Services Negotiating Committee)[48]

Situations	Suggested Questions
Introduction with opening questions Prompt the patients to bring out any issues	• How are you getting on with your medicines? • Any problems or concerns with medicines as taking/using the medications? • How do you take or use each of these medicines? (For inhalation devices users to demonstrate their use)
Identify any potential problems and concerns Provide rational explanation of how it helps their conditions	• Do you think they are working? • Any difference to what you were expecting? • Do you think you are getting any side effects or unexpected effects?
Checking the medication adherence of patients If no, follow up if it is intentional, appropriate, know if patients know the medication is necessary	• People often miss taking doses of their medicines, for a wide range of reasons. Any missing dose or change as taking it? If yes, when is the last time of doing so?
Before ending MUR	• Do you have anything else you would like to know about your medicines or is there anything you would like me to go over again? • Are you happy with the information you have on your medicines?

New Medicine Service

NMS is designed for patients prescribed with new chronic medications.[26] Research has suggested that, for these groups of patients, after 10 days, 66% reported difficulties and 61% expressed an enormous and sustained need for further information.[27] NMS is currently available for particular conditions: asthma, type 2 diabetes, warfarin, hypertension and chronic obstructive pulmonary disease. Long-term medication adherence requires a combination of strategies including instructions and counseling about the regimen.[28] Pharmacists provide patients with tailored information and advice on the use of their newly prescribed drugs during the first two months of initiating the new medication.[26] The process is illustrated in **Figure 1**.

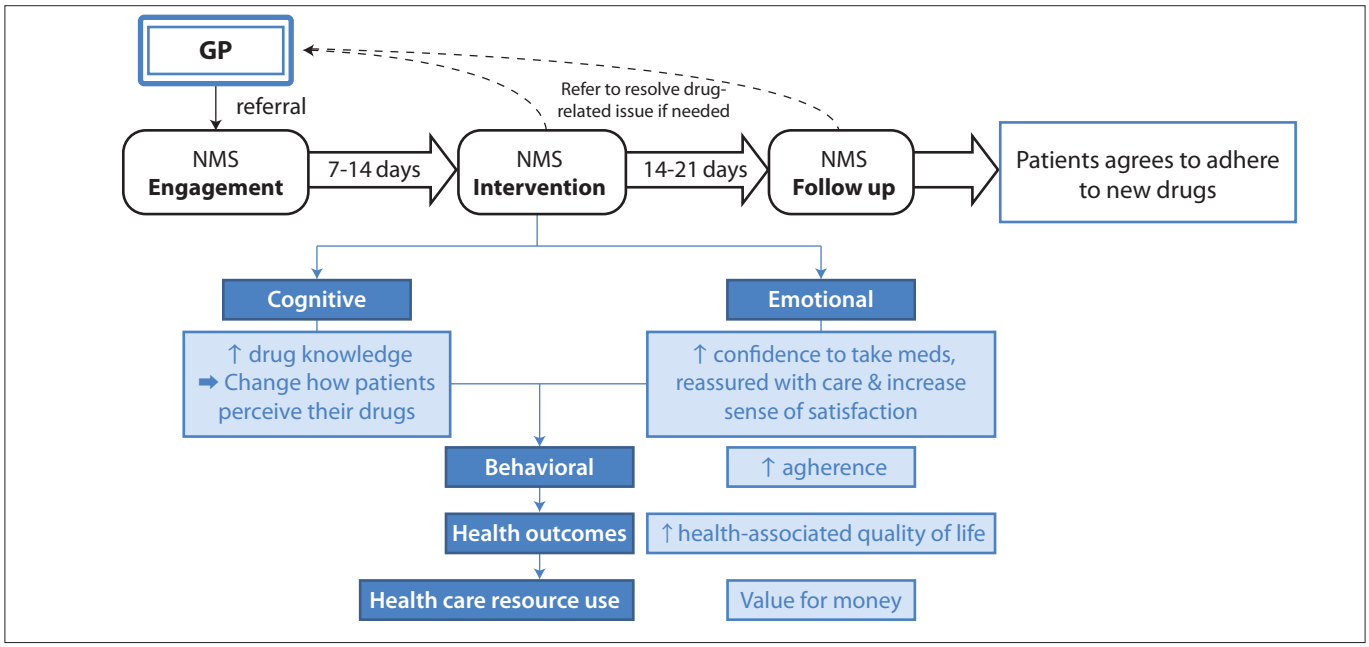

Figure 1. *The flowchart of New Medicine Service (NMS) process and the outcome (Modified from Elliott et al)*[30]

To investigate the effectiveness of NMS, a randomized controlled trial was conducted in 57 community pharmacies in England.[29] Elliott and colleagues concluded that NMS has been demonstrated to increase medication adherence significantly, with the saved cost in NHS greater than the extra cost of service. Their economic evaluation suggested NMS was a cost effective way to provide better patient care in long-term. Their qualitative study demonstrated that NMS was well-received by patients and stakeholders.[30]

Locally commissioned services

Locally commissioned services are enhanced pharmaceutical services that are initiated intending to meet relevant health needs of local population. The local areas are divided according to around 80 Local Pharmaceutical Committees (LPCs), which are the local organizations for the local group of community pharmacies help plan healthcare services and publish pharmaceutical needs assessments. The health needs are indicated by the life expectancy, lifestyle and the health consequences of lifestyle choice, and other consideration such as substance misuse, mental and sexual health and obesity. The types of services provided in a particular LPC are recorded in database. Pharmacists may require extra accreditations or trainings before providing these services.[19, 31]

Wide range of services has been commissioned and funded across England by organizations including local authority and CCG. As of July 2015, services provided by many LPCs include supervised administration, smoking cessation, needle and syringe programme, minor ailment service, emergency hormonal contraception, and on demand availability of specialist drugs.[32] On the contrary, some services are more LPCs/area-specific to meet the patient needs. For instance, tuberculosis directly observed therapy is provided by community pharmacists in City and Hackney LPCs, an area with a higher number of disadvantaged groups such as homeless and drug-abusers. Pharmacists provide supervision in completion of treatment (which directly increase compliance) of the TB regimen for reducing the drug resistance.[33] Enhanced service could reduce health inequalities with sustainable financial incentives and support from national framework.[34]

THOUGHTS ON COMMUNITY PHARMACIES IN ENGLAND

The community pharmacy services have advanced in the last couple of years, but the pace of change remains slow. From personal work experience in chain community pharmacies of England, most pharmacists still spend most of their time on checking prescriptions and dispensing medications (~300-400 dispensing items/day), even with help from dispensers. With frequent pop-up requests from counters and phone calls, some pharmacists manage to set daily target for MUR and NMS while meeting requirements from the commissioners. Other job responsibilities include administrative works for reimbursements and reading new guidelines or standard operating procedures (SOP) to be implemented for the services. With limited time, legally obligated essential services such as promotion of public health have to be completed at a mostly basic level. It is necessary to streamline the whole dispensary process to provide higher valued pharmaceutical services.

Making the best use of electronic IT systems can facilitate the overall process. While only 25% prescriptions using EPS at present, in the future it is projected to increase the use of EPS up to 90% of all prescriptions which eventually becomes the default option. It can help pharmacy staff to reduce the time required for reimbursement and manage stock control in an effective and efficient manner. Patients will be offered a unique token for their prescription, and they can choose any of their nominated community pharmacies to obtain their medications.[15] To further streamline to process, another measure required is to enabling the community pharmacists to access to SCR, which has been demonstrated to bring significant benefits for patients, GPs and pharmacists. It reduces signposting patients to other NHS services, mostly to GPs. SCR reduces the need to contact GPs to obtain more clinical information for more effective treatments, helped spot prescribing errors and maximized patient safety. It could also benefit patients by reducing their overall waiting time.[35]

Such enhancements, as shown in **Figure 2**, can free community pharmacists to help patients resolve urgent but non-life threatening health needs. The voice of shifting this kind of demand from higher cost A&E and GPs to community pharmacies has become louder within the NHS.[35] With long opening hours community pharmacies can be an instant access to manage minor ailments and emergency supply of prescribed medication through NHS. Research suggested Pharmacy-based minor ailment schemes consultations were less expensive and effective as indicated by high symptom-resolution and low reconsultation rates,[37-38] and showed to reduce more half of the use of GP consultation.[39]

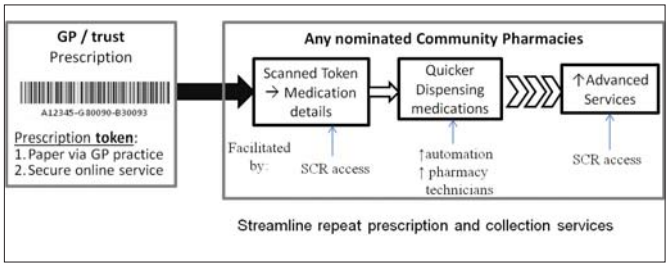

Figure 2. *Streamline the prescription-dispensing process with Electronic Prescription System (EPS) and Summary Care Record (SCR) access*

Pharmacists have increasing opportunities to lead patient self-care with more pharmaceutical products reclassification from POM to P. This increases the public convenience and access to safe and quality medications as being sold under the supervision of pharmacists.[40] Reclassified medications should be used under specific indications, dosages, packaging and pack sizes.[41] Examples include Simvastatin for hypercholesterolemia (one of the first-in-world switches in England)[42] and Orlistat (first switch by European Medicine Agency).[40] **(Table 2)** More POM-to-P switch can provide wider drug options for community pharmacists to treat patients during consultations of advanced services if needed.

We believe community pharmacists can reduce pressure of GP practice and A&E to focus on resolving more acute and complex medical cases, and hence more cost-effective health services in NHS. More specific researches on community pharmacies are required to demonstrate the cost-effectiveness of pharmacist interventions. This will sustain the funding and resources for conducting more advanced services and expanding enhanced services for specific area locally, which in turns allowing more time on their advisory role in health promotion and counseling.

Table 2. Selected POM-to-P switch in past 12 years (Adopted from Proprietary Association of Great Britain)[40]			
Year of switch	**Product name**	**Indications**	**Remarks**
2003	**Omeprazole** 10mg tablets	Relieving heartburn and acid reflux	Max period of 4 weeks
2004	**Simvastatin*** 10mg tablets	Hypercholesterolemia	-
2005	**Chloramphenicol** 0.5% eye drop	Acute bacterial conjunctivitis	For children aged 2 years or over
2006	**Sumatriptan*** 50mg tablets	Migraine	Max period of 1 day
2006	**Amorolfine** hydrochloride 5% (topical)	Fungal nail infection	For cases up to 2 nails infected
2007	**Levonorgestrel** 1.5mg tablet	Emergency hormonal contraceptive	Dose increased from 2001 approval (0.75mg)
2008	**Naproxen** 250mg tablets	Primary dysmenorrhoea	For women aged 15-50 years
2008	**Azithromycin*** 500mg tablets	Chlamydia	Taken as single 1g dose
2009	**Tamsulosin hydrochloride*** 0.4mg	Benign prostatic hyperplasia	Men aged 45-75 years
2009	**Orlistat** 60mg #	Weight loss in adult	For adults with BMI≥28 with lower-fat diet
2010	**Tranexamic Acid** 500mg tablets	Heavy menorrhagia	Max 4 days
2012	**Ibusol lotion**	Mild-to-moderate sunburn pain	-
2013	**Esomeprazole** 20mg #	Reflux symptoms	Used up to 2 weeks (reclassified to GSL in 2015)
2015	**Ulipristal Acetate**	Emergency hormonal contraceptive	Taken within 5 days if without successful contraceptions

*First switch in the world;[42] #centrally authorized European switch

PROSPECT OF COMMUNITY PHARMACY IN HONG KONG

Contrary to England, the population in Hong Kong generally receives prescribed drugs directly from private physicians or pharmacies in government clinics, without the separation between prescribing and dispensing. The community pharmacies in Hong Kong are currently underused and not government-funded, with only 1/5 to 1/50 of the dispensing volume in England per pharmacy each day. The users of local community pharmacies are usually patients who can afford branded medications which are usually more expensive. **(Table 3)** People including physicians have little understanding toward the pharmaceutical care and the profession.[43] This could explain why self-care to be led by pharmacists is not highly supported by the public and the physicians, though the majority of the local population agreed with self-care approach in chronic diseases.[44]

Table 3. General differences of chain pharmacies between England and Hong Kong		
	England	**Hong Kong**
Average dispensing volume	100-1,000 items per day	< 20 items per day
Medication availability	Wide range	Sufficient
Control Drug availability	In most pharmacy	Not always available
Second checking	Nearly all prescriptions	Not possible if no dispensers on duty
Consultation Room	Available in most pharmacies	Not available
Team members	Team of 2-10 (Pharmacists, technicians, dispensers, healthcare assistants)	1-2 (Pharmacists & Dispensers)
Number of wholesalers	~10	~30
Medication Delivery Schedule from Wholesale	1-2 times daily	Vary from the next day to 2 days
Funding system	National service	Private service
Major income	Dispensing, Advanced and Enhanced Service	Dispensing and OTC Sales
Service User	General public	Usually for people can afford more expensive branded medication
Control of New Pharmacy entry	Yes	No

Local study identified over one-third of elderly patients with chronic diseases had drug non-adherence problem, which was associated to risk factors including self-perceived adverse effects and the use of respiratory drugs.[45] Research demonstrated periodic phone counseling by Hong Kong pharmacist can significantly increase medication compliance and lower the mortality in patients receiving multiple chronic medications.[46] With people aged 65 or above expected to hit 31% in 2036,[47] community pharmacies can contribute to reduce the burden from primary healthcare by educating the patients and optimizing the use of their chronic and high-risk medications.

In practical sense, community pharmacies in Hong Kong can establish the advisory roles and be a trustworthy source of health information to promote better public health such as minor ailments. Considering the healthcare system in Hong Kong is different from that of England, it is sensible to aim at positioning the service for patients with chronic diseases that requires non-urgent but long-term medication management. If chain pharmacies consider developing similar services like MUR and NMS, the set of resources are needed to meet for the success. These include the close collaborations and trust between pharmacists and with private doctors; accessibility of Summary Care Record to tailor consultation for specific patients; and proper facilities in pharmacies such as a quiet room for private consultation to maximize the patient's confidentiality; and importantly, the support from government and the promotion of the expanded role of pharmacists to general public.

CONCLUSION

The evolving practice of community pharmacists in England has been well supported by the government with financial incentives, from the essential dispensing services to expanding advisory roles in advanced services (MUR and NMS) and the locally-enhanced services, which can be streamlined by the Electronic Prescription System and access of Summary Care Record. These services can reduce the pressure of GP practice and A&E, and facilitate more cost-effective health services in NHS. In Hong Kong, the local community pharmacists are underutilized. Despite a different healthcare system and pharmacy practice, the local community pharmacies can help promote public health and progressively enhance the present services for patients with long-term medications. With increasing medical burden, it is desirable for the local government to provide more support and utilize community pharmacies to help provide cost-effective and quality health services in Hong Kong.

Author's background

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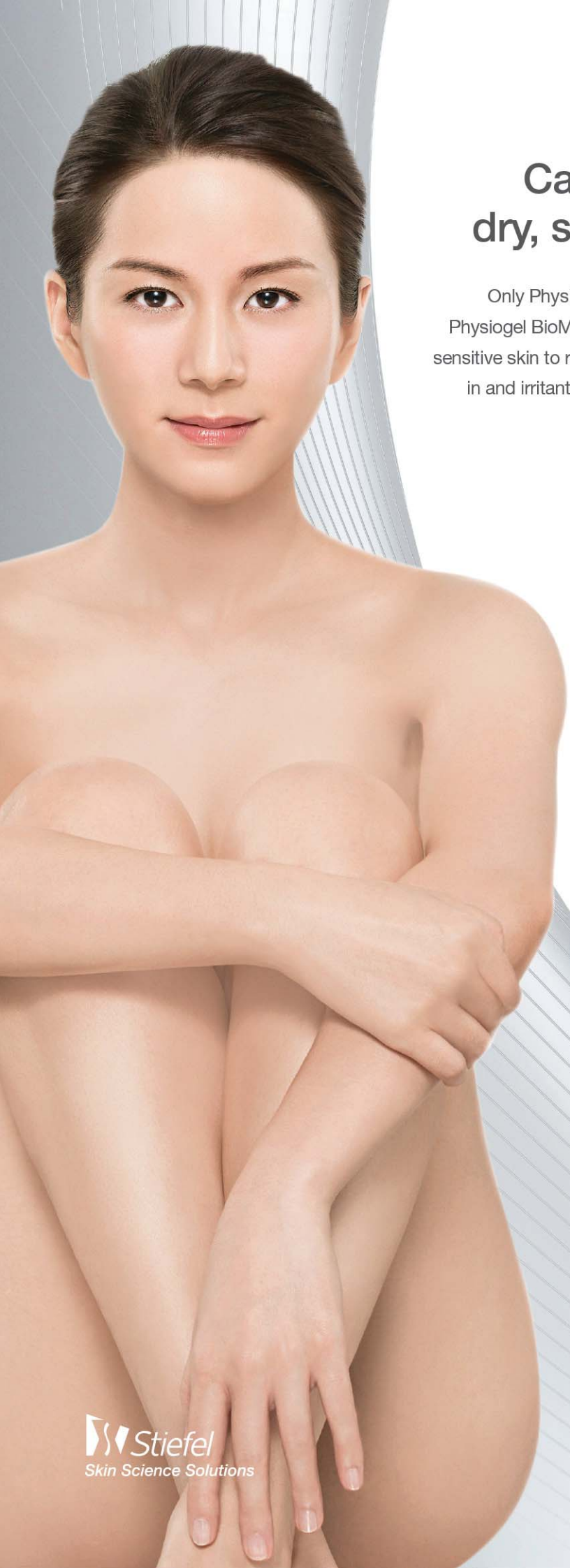

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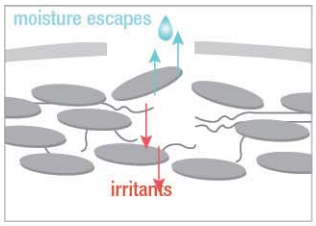

After:
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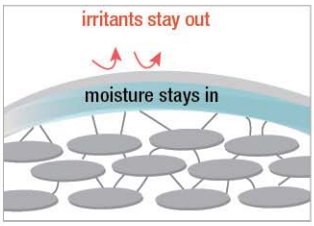

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From Aerodynamics to Inhalation Technique - More about Inhaled Medications

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ABSTRACT

Currently, it is standard practice for patients to be prescribed inhalers, especially for respiratory conditions like asthma and chronic obstructive pulmonary diseases. Compared to oral therapy, inhalation therapy is preferred for its faster onset of action with minimal systemic side effects. The popularity of inhalation therapy can be shown by the variety of inhalers, such as pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), soft mist devices (e.g. Respimat®) and nebulizers that are commercially available. In order to facilitate optimal drug delivery, contributing factors, such as device design, inhaler formulation and the patient's inhalation techniques should be addressed. With particular focus on pMDIs and DPIs, this article is aimed at illustrating aerosol drug delivery science and the importance of patient inhalation technique. To further optimise drug delivery and lung deposition, it is essential that an inhaler be formulated with the optimal particle size distribution. Together with correct inhalation technique, the best clinical outcomes of inhalation therapies can be achieved. It is also of paramount importance that physicians personalise inhalation therapies by evaluating patients' clinical responses, inhalation techniques and preferences. Hence, the most appropriate inhaler could be chosen for patients to optimise inhaled drug efficacy.

Keywords: *Inhalers, Lung deposition, Inhalation technique, pressurized metered-dose inhalers, dry powder inhalers*

INTRODUCTION

In patients with respiratory conditions such as asthma and chronic obstructive pulmonary disease, inhalation therapies are the most commonly prescribed medications. These medications, including short-acting β_2-adrenergic agonists (SABA), long-acting β_2-adrenergic agonists (LABA), anti-cholinergics, and inhaled corticosteroids (ICSs), have been formulated as aerosols to facilitate direct delivery to the lungs. The targeted drug delivery not only provides a faster onset of action for bronchodilator agents, but also causes less systemic side effects. Today, the variety of commercially available inhalation devices is increasing and some examples are pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), soft mist devices (e.g. Respimat®) and nebulizers.

Generally, a patient's response to a drug can be attributed to the pharmacodynamic and pharmacokinetic profile of the drug. However, in inhalation therapy, drug effect is distinctly affected by the physical sciences that underlie the unique device design, the inhaler formulation, and the patient's inhalation technique. This article introduces the scientific basis behind aerosol drug delivery and the implications for patient inhalation technique, with particular focus on two commonly used inhaler types, namely, pMDIs and DPIs.

PARTICLE SIZE, AERODYNAMIC AND LUNG DEPOSITION

Drug delivery via the airways is more complex than oral therapy. Inhaled drug particles deposit into the respiratory tract via three mechanisms; inertial impaction, sedimentation, and diffusion **(Figure 1)**.[1] Due to high inertia, large drug particles, especially those with diameter >5μm, are unable to change direction with the airstream and reach the lower airways. They are likely to impact onto the oropharynx and be swallowed; or impact onto the upper large bronchial tree. This process is known as inertial impaction. On this account, minimal proportion of large particles in inhaled corticosteroids is critical to reduce local adverse effects such as oral candidiasis.[2]

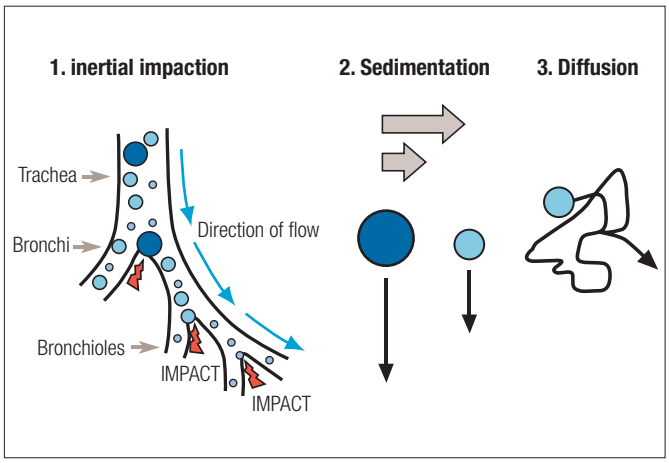

Figure 1. *The mechanisms of particle deposition in respiratory tract. Adapted from (1) with permission*

In contrast, drug particles of smaller size can go further down the airway by sedimentation and diffusion. The proportion of particles with diameter <5μm is known as fine-particle fraction (FPF) or fine-particle dose (FPD) if expressed as the absolute mass. The smaller the particle size, the more the particles can deposit in the peripheral airways and even the alveolar region by gravitational sedimentation, thereby producing the desired clinical response. Some ultrafine particles with a 0.1-1μm size range diffuse by Brownian motion, i.e. random movement, and deposit in the airway wall after collision. However, this diffusion process only accounts for about 1% of the total drug deposition as they are light-weight and can be easily exhaled.[1,3,4] The relationship between drug particle size and lung deposition is summarised in **Figure 2**.[5,6] Undoubtedly, an inhaler product needs to be formulated with the optimal particle size distribution to achieve the best clinical response.

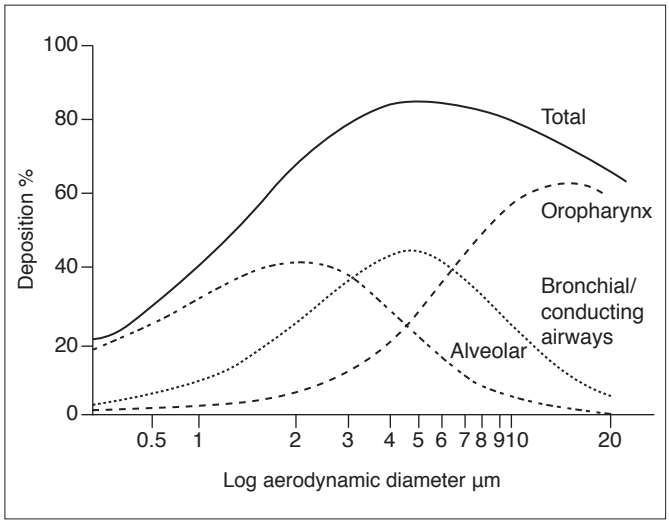

Figure 2. *Relationship between aerodynamic diameter and lung deposition. Adapted from (5) and (6) with permission*

Pressurized metered-dose inhalers

A pMDI consists of a canister, a metering chamber, and an actuator with a mouthpiece. The medication is stored in the pressured canister with a liquefied gas propellant, which is most frequently hydrofluoroalkane (HFA). Shaking the device before use is necessary to generate the pressure for medication aerosolisation and to mix the liquefied gas propellant with the medication solution. Once the pMDI is compressed, the drug is ejected together with the HFA propellant. As the propellant evaporates, the aerosolised drug particles diminish in size and deposit into the respiratory tract.[7]

Patients using pMDIs should be educated to inhale slowly and deeply, and hold their breath for 6-10 seconds afterwards. As pMDIs are formulated to eject drugs as an aerosol at high velocity with the use of a propellant, fast inhalation would only further increase aerosol velocity, causing more oropharyngeal impaction and reduced drug penetration to the peripheral airways.[8] A study by Usmani OS *et al* revealed that fast inhalation shifts the aerosol distribution to the upper airways.[9] Breath-holding after aerosol inhalation is important because it increases the residence time of the inhaled particles to allow more time for the sedimentation and diffusion processes; enhancing deposition of drug particles into the peripheral airways.[10]

The hand-breath coordination is one of the major limitations of the pMDI. Studies demonstrate that early firing of the device by even 0.5 second or delayed firing relative to the onset of inspiration would greatly reduce lung deposition by up to 34% and 41% respectively.[11] Therefore, the patient's ability to coordinate device actuation and inhalation must be assessed before starting a pMDI. A spacer can be considered for patients who fail to demonstrate the coordination technique.

In addition to eliminating the need for hand-breath coordination, a spacer also increases the travel distance of the aerosol from the pMDI to the oropharynx, allowing more propellant to evaporate. With a reduction in drug particle size, less oropharyngeal deposition and a higher proportion of peripheral drug delivery can be achieved. Nevertheless, spacers are generally more bulky and can be associated with accumulation of electrostatic charges on the plastic wall, which may limit performance. To minimise accumulation of electrostatic charges, the spacer should be regularly and appropriately cleaned according to the manufacturer's recommendation. Patients should still be advised to inhale slowly and hold their breath when using a spacer with a pMDI.[6]

Dry powder inhalers

DPIs are formulated either as multi-dose or single-dose capsule devices. The multi-dose type can be further divided into two formulations. One contains a bulk formulation with a drug reservoir metered by the patient upon use (e.g. Turbuhaler® for Symbicort); the other contains a pre-metered dose in blistered packaging within the device (e.g. Accuhaler® for Seretide). Examples of single-dose DPIs are Handihaler® (e.g. Spiriva) and Breezhaler® (e.g. Onbreez).[6]

DPI is composed of a medication reservoir, an air inlet, a de-agglomeration compartment and a mouthpiece. The drug is stored either in a pure form or bound to an inert large carrier molecule to form loose agglomerates. To optimise drug particle size for lung deposition, patients need to produce a sufficient inspiratory flow to generate the required turbulence for de-aggregating the drug agglomerates.[12] The faster the flow, the higher the turbulent energy generated, and the more effective the particle de-aggregation.[13]

Owing to the breath-actuated nature, DPI gives an advantage in eliminating the need for hand-breath coordination. Nonetheless, DPI should only be prescribed to patients with a minimum inspiratory flow of 30L/min.[14] This is especially important for patients with severe airflow obstruction, young children and the elderly.[15] Contrary to pMDIs which should be inhaled slowly and deeply, DPIs should be inhaled forcefully and deeply in order to create sufficient initial energy for more effective drug deposition into the lungs. While using capsule DPI, the inhalation process should be long enough to empty the capsule and provide a prolonged dose emission. In fact, the manufacturer of Handihaler recommends the inhalation is repeated to ensure that the full dose is emitted.[16]

Selection of inhalers

A number of factors should be considered when selecting an appropriate inhaler device. The choice of inhaler device should be personalised according to the patient's clinical condition, their ability to use the device effectively, and their preference. **Table 1** compares pMDIs and DPIs and highlights the most important inhalation techniques for effective use. Apart from pMDIs and DPIs aforementioned, the reader should bear in mind that other devices not described in this article (e.g. soft mist inhalers, nebulisers) are available on the market. **Table 2** show examples of inhaler devices that are available in the Hospital Authority drug formulary and briefly compares drug delivery characteristics such as particle size and lung deposition.

Table 1. Comparison of pMDIs and DPIs[6,17,18]

Inhaler	Advantages	Disadvantages	Inhalation Techniques
pMDIs	- Portable and compact - Not dependent on peak inspiratory flow - Low contamination risk in a closed system	- Hand-breath coordination needed (Spacer can be considered in patients with difficulty in hand-breath coordination) - Lack of dose counter in most devices	- Shake before use - Inhale slowly and deeply - Keep device upright during use - Hold breath for 6-10 seconds - Require priming if device is new or not used for certain time
DPIs	- Portable and compact - Breath-activated (hand-breath coordination not necessary) - Dose counter available	- Dependent on peak inspiratory flow - More costly	- Inhale forcefully and deeply - Keep device upright or horizontal during use - Require drug loading - Inhale twice for capsule device - Do not exhale into the device after drug loading

Table 2. Characteristics of available inhalers in the Hospital Authority drug formulary

Drug Name	Brand Name	Strength Available	Drug Class	Device Information	Particle Size	Lung Deposition
Pressurized metered-dose inhaler (pMDI)						
BECLOMETHASONE DIPROPIONATE [Hong Kong Medical Supplied Ltd]	/	50mcg/dose 250mcg/dose	Corticosteroids	HFA 134A as propellant[19]	0.9 micron[20],a	~ 50%[20, 21],a
BECLOMETHASONE DIPROPIONATE & FORMOTEROL FUMARATE [Zenfields (H.K.) Limited]	Foster	100/6mcg	Corticosteroids + LABA	HFA 134A as propellant[22]	Beclomethasone: 1.3±0.1μm[23] Formoterol: 1.4±0.1μm[23]	34.08±9.30% (relative to nominal dose) in healthy subjects, 30.86±8.89% in asthmatics, and 33.10± 8.90% in COPD patients[24]
BUDESONIDE & FORMOTEROL [AstraZeneca]	Vannair	160/4.5mcg 80/4.5mcg	Corticosteroids + LABA	HFA-227 as propellant[25]		
CICLESONIDE [Takeda Pharmaceutical]	Alvesco	80mcg/dose 160mcg/dose	Corticosteroids	HFA 134A as propellant[26]	1μm[26]	52±11%[27]
FLUTICASONE PROPIONATE [GlaxoSmithKline]	Flixotide	50mcg/dose 125mcg/dose 250mcg/dose	Corticosteroids	HFA 134A as propellant[28]		
FLUTICASONE PROIONATRE & FORMOTEROL FUMARATE DIHYDRATE [Mundipharma]	Flutiform	50/5mcg 125/5mcg 250/10mcg	Corticosteroids + LABA	HFA 227 as propellant[29]	Fluticasone: At 28.3 L/min: 3.52±1.59μm At 60.0 L/min: 3.15±1.77μm[30] Formoterol: At 28.3 L/min: 3.52±1.56μm At 60.0 L/min: 3.17±1.71μm[30]	44%[31]
IPRATROPIUM BROMIDE [BoehringerIngelheim Ltd]	Atrovent	20mcg/dose	Anti-muscarinic bronchodilator	HFA 134A as propellant[32]	Fine particle fraction <5μm: 30.9%[33] Extra fine particle fraction <1μm: 20.7%[33]	10–30%[32]
SALBUTAMOL (SULPHATE) [GlaxoSmithKline]	Ventolin	100mcg/dose	SABA	HFA 134A as propellant[34]	2.29μm[35],a	10%[36]
SALMETEROL (XINAFOATE) [GlaxoSmithKline]	Serevent	25mcg/dose	LABA	HFA 134A as propellant[37]	Fine particle fraction (1.1–4.7μm): 34.8–40.4 %[38]	
SALMETEROL & FLUTICASONE [GlaxoSmithKline]	Seretide Lite Seretide Medium Seretide Forte	25/50mcg 25/125mcg 25/250mcg	Corticosteroids + LABA	HFA 134A as propellant[39]	~ 2.7μm[40],a	~ 16%[40],a

Drug Name	Brand Name	Strength Available	Drug Class	Device Information	Particle Size	Lung Deposition
Dry powder inhaler (DPI)						
BUDESONIDE [AstraZeneca]	Pulmicort	100mcg/dose 200mcg/dose	Corticosteroids	Multi-dose Turbuhaler	30L/min flow rate: 3.2μm[41] 60L/min flow rate: 2.9μm[41] 90L/min flow rate: 1.8μm[41]	32%[42]
BUDESONIDE & FORMOTEROL [AstraZeneca]	Symbicort	80/4.5mcg 160/4.5mcg 320/9mcg	Corticosteroids + LABA	Multi-dose Turbuhaler	Budesonide : 2.2μm[43] Formoterol : 2.4μm[43]	Budesonide: 32–44%[44] Formoterol: 28–49%[44]
TERBUTALINE SULPHATE [AstraZeneca]	Bricanyl	0.5mcg/dose	SABA	Multi-dose Turbuhaler		22%[45]
SALMETEROL & FLUTICASONE [GlaxoSmithKline]	Seretide 100 Seretide 250 Seretide 500	50/100mcg 50/250mcg 50/500mcg	Corticosteroids + LABA	Multi-dose Accuhaler	Fine particle fraction: Fluticasone: 20.4%[46] Salmeterol : 18.4%[46]	11–15%[47]
VILANTEROL & FLUTICASONE [GlaxoSmithKline]	RelvarEllipta	100/25mcg 200/25mcg	Corticosteroids + LABA	Multi-dose Accuhaler		Fluticasone: ~15.2%[48] Vilanterol: ~27.3%[48]
GLYCOPYRRONIUM [Novartis]	Seebri	50mcg/cap	Anti-muscarinic bronchodilator	Single-dose Capsule inhaler	2.8μm[49]	40%[50]
INDACATEROL (MALEATE) [Novartis]	Onbrez	150mcg/cap 300mcg/cap	LABA	Single-dose Capsule inhaler	3.2μm[51]	31%[51]
TIOTROPIUM (BROMIDE) [BoehringerIngelheim Ltd]	Spiriva	18mcg	Anti-muscarinic bronchodilator	Single-dose Capsule inhaler	3.9μm[51]	22%[51]
Soft mist inhaler						
TIOTROPIUM (BROMIDE) [BoehringerIngelheim Ltd]	Respimat	2.5mcg/dose	Anti-muscarinic bronchodilator	/	Mostly < 2.1μm[52]	37% in untrained patients; 53% in trained patients[53]

Definition of abbreviations: CFC: Chlorofluorocarbon; HFA: hydrofluoroalkanes; LABA: long-acting beta-2 agonist; mcg: microgram; SABA: short-acting beta-2 agonist
Data are referenced from package inserts and/or published reports where available and are not meant to be exhaustive. For further information and clarification, the manufacturer and/or supplier should be consulted.
[a] Data cited are extrapolated from published report(s) on the inhaler product that is described to contain the same active ingredient(s) and use the same inhalation device; thus data may not be brand-specific.

CONCLUSION

The aerodynamics of the inhaled medication, the drug delivery mechanism of the inhaler device, and patients' inhalation technique are important factors contributing to the efficacy of an inhaled drug. Incorrect use of inhaler device is not uncommon; and adversely affects patients' clinical response.[16] To enhance drug effectiveness, it is crucial to assess the patient's condition and cognitive function, individualise regimes, provide education on inhalation technique, regularly review adherence, and avoid prescribing different types of device or frequently changing device for a single patient.[6] Only with better understanding of the theories behind the delivery of inhaled medications can healthcare professionals choose the most appropriate inhaler devices for patients and provide optimum patient education.

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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.)

2 CE Units

From Aerodynamics to Inhalation Technique - More about Inhaled Medications

1) Which of the following lung deposition processes contributes mostly to the clinical response of inhaled medication?

A. Inertial impaction
B. Sedimentation
C. Diffusion
D. Brownian motion

2) Which of the following define fine particle fraction (FPF)?

A. Ultrafine particles with size range 0.1-1μm
B. Particles with size range 1-5μm
C. Particles with diameter <5μm
D. Particles with diameter >5μm

3) Which of the following is/are component(s) of a pressurized metered-dose inhaler (pMDI)?

A. Actuator
B. Liquefied gas propellant
C. Metering chamber
D. All of the above

4) Which of the following is NOT a proper way of using pMDI?

A. Start inhalation at the same time with device actuation.
B. Inhale deeply.
C. Inhale quickly.
D. Hold the breath for 6-10 seconds after inhalation.

5) Which of the following is/are advantage(s) of using a spacer together with pMDI?

A. Elimination of the need for hand-breath coordination
B. Elimination of the need for breath holding after inhalation
C. Accumulation of electrostatic charges
D. All of the above

6) Which of the following is NOT a formulation of dry powder inhalers (DPIs)?

A. Accuhaler®
B. Breezhaler®
C. Respimat®
D. Turbuhaler®

7) Which of the following is/are proper way(s) of using DPI?

A. Inhale deeply.
B. Inhale quickly.
C. Inhale long enough when using capsule DPI.
D. All of the above.

8) Which of the following statements is incorrect?

A. The proportion of large particles in inhaled corticosteroids should be maximized to reduce local adverse effects.
B. Shaking pMDI before use helps generate the pressure for medication aerosolization and mix the liquefied gas propellant with the medication solution.
C. A spacer should be regularly and appropriately washed in order to minimize accumulation of electrostatic charges.
D. Patient's inspiratory flow should be assessed before prescribing DPI.

9) Patient X is an 80 year-old male with severe airflow obstruction and difficulty in hand-breath coordination. The doctor wants to prescribe an inhaled bronchodilator. Which of the following formulation is most suitable for him?

A. pMDI
B. pMDI with spacer
C. Handihaler®
D. Turbuhaler®

10) Which of the following will enhance drug effectiveness of inhaled medications?

A. Assess patient's conditions and cognitive function before prescribing.
B. Provide education on inhalation technique.
C. Avoid prescribing different types of device or frequently changing device for a single patient.
D. All of the above.

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 222(D&T)

General Overview of Novel Oral Anti-Coagulants

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

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Biosimilar Products of Recombinant Human Granulocyte Colony Stimulating Factor in Reference to Neupogen

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ABSTRACT

Human granulocyte colony stimulating factor (hG-CSF) is a 174-amino-acid protein that is known to have effects on myelo-proliferation. The stimulating factor is extensively used to treat neutropenia. Recent studies have shown that the factor is also effective on stimulating for hematopoiesis, stem cell mobilization, neurogenesis etc. Hence, there is a great demand for hG-CSF. Since the molecular sequence of endogenous hG-CSF was identified in the 1980s, different recombinant human G-CSF (rhG-CSF) have been produced using different biotechnological processes. Consequently, products of rhG-CSF differ from each other by their protein sequences and non-proteinaceous side groups and presumably some minor differences in biochemical properties except for the same clinical effects. This review article attempts to provide an insight by comparing their chemical structures and some efficacy data of these different rhG-CSF currently available in the market and contrast the suitability of these biosimilar products to Neupogen, which is regarded as a reference hG-CSF.

Keywords: *human granulocyte colony stimulating factor, neutropenia treatment, biosimilar drugs, biotechnological process, rhG-CSF, Neupogen, efficacy of biopharmaceuticals, quality assurance*

INTRODUCTION

Neutropenia is a blood disorder due to an unusually low number of neutrophils in the blood.[1,2] It could be life-threatening. Although it occurs for various reasons, there have been many recent advances in our understanding of the molecular basis of neutropenia disorders. Molecular and cellular studies now suggest that accelerated apoptosis of neutrophil precursors in the bone marrow is the common pathophysiologic cause.[3] Neutrophils, which derive from stem cell of the bone marrow and make up the major part of the granulocytes, are a type of white blood cells in the circulation system. They are important as they defense the body against harmful foreign bodies like bacteria and cellular debris **(Figure 1)** by phagocytosis and proteolysis.[4] A patient with too few neutrophils is more susceptible to bacterial infections. The risk of infection increases if low neutrophil counts persist.

Patients who suffer from cancers may become neutropenic because of the chemotherapy they receive causes the problem lacking neutrophils matured in the bone marrow.[3-5] Destruction of neutrophils outside the bone marrow can also be a causation. Other possibilities are post-infections from viruses such as Epstein-Barr virus, cytomegalovirus, Human Immunodeficiency Virus, hepatitis viruses, *etc.*; exposure to high dose of radiation; taking certain medications, such as antibiotics, blood pressure regulating drugs, psychiatric drugs, epilepsy drugs, etc.; or simply because of nutritional deficiency. However, some other causes for neutropenia are merely uncertain.[4,6]

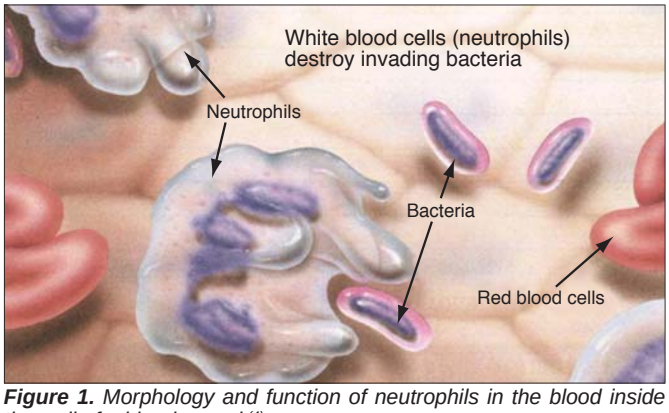

Figure 1. *Morphology and function of neutrophils in the blood inside the wall of a blood vessel.*[4]

Symptoms in mild neutropenia are not obvious. People may only learn they have got neutropenia after blood tests or bone marrow examinations were conducted **(Figure 2)**. But people may have other symptoms from infection or the underlying problem causing severe neutropenia, particularly when the absolute neutrophil count persistently falls below 500 per ml for more than three days. Infections occur most often in the mucous membranes, such as the inside of the mouth and the skin. They can appear as ulcers, abscesses, rashes and open wounds that take longer than usual to heal. Furthermore, fever is also a common symptom of the inflammation caused by neutropenia.[4] The duration and severity of neutropenia directly correlate with the total incidence of all infections and of those infections that are life threatening. Tuberculosis is one type of infection that may cause neutropenia.

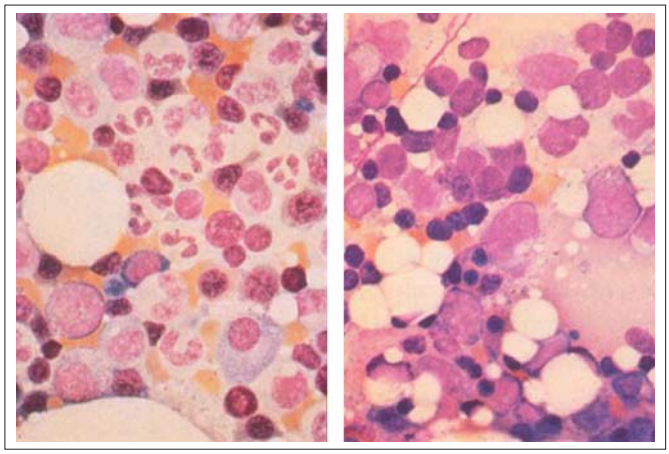

Figure 2. *A typical bone marrow of a patient with severe congenital neutropenia showing the absence of mature neutrophils (right) compared to the bone marrow of a healthy individual with neutrophils at all stages of maturation (left).*[4]

Treatment for neutropenia

The treatments that are still on trials and/or are being adopted for managing the condition of neutropenia, include (1) granulocyte-colony stimulating factor (G-CSF);[7] (2) bone-marrow transplant (BMT);[8] and (3) others such as cytokines, antibiotics, vitamins, immunosuppressive drugs, immunoglobulins corticosteroids and white blood cell transfusion.[9]

CHEMICAL STRUCTURE OF NATURAL G-CSF

Natural G-CSF is a glycoprotein. It stimulates the bone marrow to produce granulocytes and stem cells, which are then released into the bloodstream. It is a cytokine, hormone as well as a hematopoietic growth factor of myeloid lineage, produced by endothelium, macrophages, and a number of other immune cells in the human body.[10] The natural human glycoprotein was identified in the 1980's.[11] It exists in two forms, the 174- and 177-amino acid long. The latter has a molecular wight of 19,600 kDa. It is more abundance and more active than the 174-amino acid form. It has been used in the development of pharmaceutical products by recombinant DNA (rDNA) technology.

The G-CSF-receptor is present on precursor cells in the bone marrow, and, in response to stimulation by G-CSF, initiates proliferation and differentiation into mature granulocytes. G-CSF is also a potent inducer of HSCs mobilization from the bone marrow into the bloodstream, although it has been shown that it does not directly affect the hematopoietic progenitors that are mobilized.[10]

Besides the effect on the hematopoietic system, G-CSF can also act on neuronal cells as a neurotrophic factor. Indeed, its receptor is expressed by neurons in the brain and spinal cord. The action of G-CSF in the central nervous system is to induce neurogenesis, to increase the neuroplasticity and to counteract apoptosis.[10,12] These properties are currently under investigations for the development of treatments of neurological diseases such as cerebral ischemia.

Human G-CSF is constructed by a structural motif called 4-α-helix bundle, which has 4 α-helical chains in antiparallel fashion. The bundle of the chains has left-handed twist. Within the bundle, the 4 helices are referred as helices A to D and the connecting loops are called AB, BC, and CD loops. The AB and CD loops are long overhand connections whereas the BC loop is short hairpin loop.[13] It has been proven that the two disulphide bonds in the molecule are essential for the biological activity of HG-CSF. They are Cys36-Cys42 and Cys64-Cys74 respectively. Cys64-Cys74 also contribute to the α-helix structure stability. Without this bond, only half of the native structure of the α-helix could be formed.[14] There is another cysteine – Cys17 which is free from disulphide linkage. G-CSF, which is given as treatment is not from human beings but is safely made by industrial processes by recombinant DNA techniques to produce an identical substance that has all the normal activity and function of the naturally occurring cytokine. Compared to recombinant hG-CSF, natural G-CSF has minimal glycosylation – only O-glycosylated at Threonine-133 position. This glycol-chain has no significant contribution to the 3D structure of the protein.[15]

Physiological Role of hG-CSF

The major physiological roles of hG-CSF are stimulating granulogenesis, neurogenesis and anti-apoptosis.[10] hG-CSF is released by monocytes, macrophages, endothelial cells fibroblasts, astrocytes and a number of other immune cells, all of which are related to the defense system in the body, to blood or to cells nearby. The target cells are hematopoietic progenitors which are committed to the neutrophil lineage, monocytes, blood platelets, neurons, endothelial cells. When G-CSF reach the target cells, they bind to cytokine receptors of the cell surfaces, which assembly to initiate downstream signaling pathways, including JAK-STAT (Janus kinase – Signal Transducer and Activator of Transcription), MAPK (mitogen-activated protein kinase)/ERK (extracellular signal-regulated kinase) Akt pathways. JAK-STAT signaling pathway results on activation of gene promoters, initiating gene transcription. Both MAPK/ERK and Akt pathways take role in cell growth, progression in cell cycle. Akt pathway also takes part in cell survival and apoptosis as well as cell migration. In short, G-CSF helps survival and proliferation of cells. Indeed, it stimulates bone marrow to produce neutrophils. It is a process of how the hematopoietic progenitor cells in bone marrow are differentiated into neutrophils and allowing those granulocytes to proliferate before releasing them into blood.[16-18] It also induces growth of neurons and prevents them from apoptosis.[19]

Clinical Application

Since 1990, G-CSF was applied to increase white blood cells count and to protect from potentially lethal infections after the patient has gone through high-dose chemotherapy, radiotherapy and bone marrow transplantation. Those patients are likely to have neutropenia, which is a hematological disorder characterized by abnormal low count of neutrophils (< 1700 cells per ml of blood) for adults. When the neutrophil counts drops to less than 500 cells per ml of blood, the patient will be susceptible to opportunistic bacteria in alimentary tract (Mayo Clinic). However, upregulated production of G-CSF in response to lung cancer therapy indeed promotes the migratory and invasive properties by triggering the epithelial-mesenchymal cell transition (EMT) in non-small-cell lung cancer cells (NSCLCs).[20] In this case G-CSF is not recommended. G-CSF is also used to treat acute infection, inflammation and help in repair process. It also re-modulates the immune system by reducing the cytotoxicity of natural killer cells so as to alleviate autoimmunity and transplant rejections.[21] As G-CSF is also a neurotrophic factor, it became a direction of research on treatments of neurological diseases such as cerebral ischemia.[10,19,22]

TYPES OF G-CSF PRODUCTS DERIVED FROM GENETIC ENGINEERING

There are four types of rhG-CSF available on the market. All currently available medicinal brand products of G-CSF, as listed

Table 1. Biosimilar products of hG-CSF approved by European Medicines Agencies.					
Medicinal Brand Name	**Active Substance**	**Marketing Authorization Holder**	**Authorization Date**	**Is Biosimilar**	**Reference Product**
Accofil	filgrastim	Accord Healthcare Ltd	18/09/2014	yes	Neupogen
Biograstim	filgrastim	AbZ-Pharma GmbH	15/09/2008	yes	Neupogen
Filgrastim Hexal	filgrastim	Hexal AG	06/02/2009	yes	Neupogen
Grastofil	filgrastim	Apotex Europe BV	18/10/2013	yes	Neupogen
Nivestim	filgrastim	Hospira UK Ltd.	08/06/2010	yes	Neupogen
Ratiograstim	filgrastim	Ratiopharm GmbH	15/09/2008	yes	Neupogen
Tevagrastim	filgrastim	Teva GmbH	15/09/2008	yes	Neupogen
Zarzio	filgrastim	Sandoz GmbH	06/02/2009	yes	Neupogen
Neulasta	pegfilgrastim	Amgen Europe B.V.	22/08/2002	no	/
Lonquex	lipegfilgrastim	Sicor Biotech UAB	25/07/2013	no	/
Granocyte	lenograstim	Chugai	1993	no	/

in **Table 1**, could be grouped either as filgrastim, pegfilgrastim, lipegfilgrastim and lenograstim. They are all G-CSF with different chemical modifications – unglycosylated (filgrastim), pegylated (pegfilgrastim), pegylated with carbohydrate linker (lipegfilgrastim) or glycosylated (lenograstim).

Filgrastim

Filgrastim is the less unglycosylated rhG-CSF produced from Escherichia coli. Glycosylation was not possible in Filgrastim because the rhG-CSF is produced in prokaryotic system, which does not contain post-translation modification system. Due to the same reason, this rhG-CSF contains methionine at the N-terminal because bacterial system cannot modify the protein sequence after translation. However, bacteria has DsbA/DsbD system to catalyse the formation of disulphide bonds after the peptides are made.[23] Filgrastim can be stored for 30 months under 2 to 8°C (electronic Medicines Compendium (eMC), Specification of Neupogen 30 MU solution for injection, 2015). It uses acetate buffer system. The earliest rhG-CSF manufactured is Neupogen by Amgen, Inc., licensed in 1991. Neupogen is the reference product for all biosimilar products of unglycosylated filgrastim. The license of Neupogen just expired by 31st March, 2015[24] but numerous biosimilar products derived from Neupogen are being introduced on the market.

Pegfilgrastim

Pegfilgrastim is also produced by *E. coli* by recombinant DNA technology followed by covalent conjugation of 20 kD polyethyene glycol (PEG). Due to increased molecular size, it will take longer time before all of this drug to be removed by ultrafiltration in kidneys; therefore pegfilgrastim is the sustained duration form of filgrastim. PEGylation is also known to enhance physical stability (e.g. decreased susceptibility to proteolysis and aggregation) and increased solubility.[25] Like filgrastim, pegfilgrastim use *E. coli* as host system so there is no removal of first methionyl nor glycosylation. 10 mM Sodium acetate was chosen as buffer at pH 4.0.[26] It is noted that PEGylation is an in vitro procedure after extracting filgrastim from host cells. Pegfilgrastim can be stored for 3 years under 2 to 8°C.[27]

Lipegfilgrastim

Lipegfilgrastim is a covalent conjugate of filgrastim with methoxy polyethylene glycol (PEG) via a carbohydrate linker consisting of glycine, N-acetylneuraminic acid and N-acetylgalactosamine. Lipegfilgrastim is structurally and clinically similar to pegfilgrastim. Clinical study demonstrated that lipegfilgrastim 6 mg is as effective as pegfilgrastim in reducing neutropenia in patients with breast cancer receiving myelo-suppressive therapy.[28] Currently, there is only one lipegfilgrastim is licensed by EMA. It is called Lonquex® manufactured by Teva Pharmaceutical Industries Ltd. Lonquex also uses acetic acid as buffer system and its shelf life is 2 years when stored at 2 to 8°C.

Lenograstim

Lenograstim, commercially named Granocyte under the manufacturer Chugai, was licensed in Europe and Japan in 1993. Lenograstim is the only rhG-CSF used mammalian cell as host system, namely Chinese Hamster Ovary (CHO) cells. This allows post-translation modification to happen. The extreme N- terminal methionyl is removed so this protein is 174 amino acids long. Same as natural G-CSF, O- Glycosylation at Threonine-133 stabilizes the protein by preventing the formation of extra disulphide bonds by protecting the cysteine-17 sulfhydryl group.[29] The extra stability allows the product to be stored under room temperature instead of inside refrigerator (0 – 30°C) for 30 months.[30] Lenograstim adopts the phosphate buffer system for storage.

BIOSIMILARS OF NEUPOGEN

Biosimilar products are designed in order to save production costs so that biopharmaceuticals are more accessible by the public and the manufacturers can save the budget for further researches. Yet, still, manufacturers have to aware of potential difference in safety and efficacy between biosimilars and approved reference products. Therapeutic equivalent is defined as biopharmaceuticals with same chemical compositions and they are bioequivalent (i.e. similar pharmacokinetic profile). Therapeutic comparability implies that although the biosimilars and reference products may not be chemically identical but they have comparable efficacy and safety. It is noted that biosimilars must be therapeutic comparable but not necessarily equivalent. EMA has published guidelines that stating ANC (absolute neutrophil count) and CD34+ as indicators of clinical efficacy whereas toxicity test results, immunogenicity (formation of anti-rhG-CSF antibodies) and incidence of adverse side effects (AEs) should be monitored to determine the safety of G-CSF biosimilars.[31] The potential side effects of filgrastims are musculoskeletal pain, headache, nausea, fever[32] and splenomegaly.[33]

Before drugs being approved, biosimilar products have to go through chemical, in vitro and in vivo clinical trials/studies, then followed by on-going pharmacovigilance monitoring. The G-CSF biosimilars on the market have passed all these checkpoints, but whether they can ultimately be considered effective and safe enough for human use, they still have to be made comparing against the reference product: Neupogen. However, there are still a few statistical differences found between the biosimilars and the Neupogen; yet it was once thought the biosimilars had been within the acceptable range. These slight differences were then recorded for drug profiling, sitting there for further researches.

The manufacturing processes of innovators' products are all proprietary knowledge which are only accessible by

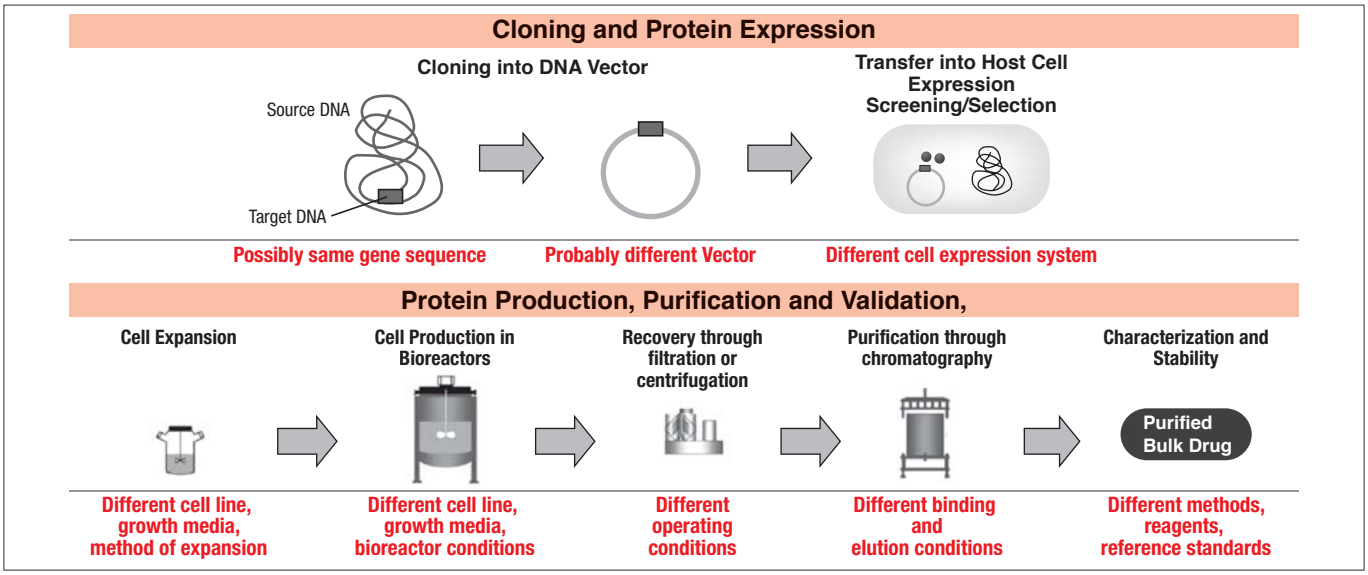

Figure 3. *Source of variation of biopharmaceutical products between manufacturers.*[34]

authorized and legitimate manufacturers of the biosimilars. This confidential knowledge or know-how is an intellectual property that is protected by trade secret laws. Therefore replicating any of the proteins not authorized is prohibited. Difference in manufacturing process may result in a variety of protein isoforms, difference in tertiary structures, acid-base variants or different glycosylation profiles. **Figure 3** shows the source of variations of biosimilars/innovator biopharmaceuticals between manufacturers. Causes of variations could be started from the very stage stages during cloning and protein expression due to some minor changes in gene sequence, use of different vector and/or expression system. But differences could also be derived from the later stages when the protein is produced, purified and validated during the production stage. These minor differences are the possible sources of variation of all biopharmaceutical products between different manufacturers.

Accofil and Gastophil

Accofil and Gastophil are relatively newly approved biosimilars. A report on both pre-clinical and clinical study summarized that in terms of safety and efficacy, and supported by pharmacokinetic and pharmacodynamic data.[35] There was no statistically difference in ANC (absolute neutrophil count) after administration of these biosimilars to patients who are receiving myelosuppressive chemotherapy when compared to Neupogen. The intra-individual variability of CD34+ cell counts in response to neutropenia treatment and stem cell mobilization was so high that this parameter should be individualized for standardization. There was no clinical evidence of anti-filgrastim antibody formation although 8 out of 185 samples showed positive result in ELISA test. It was said that the number and severity of adverse events (AE) by Accofil and Grastofil was similar to Neupogen (75% of subjects (n=36) suffered from AE after administration of Accofil/ Grastofil; 66.7% (n=36) for Neupogen; 33.3% for placebo).[35]

XM02 (Biograstim/ratiograstim/tevagrastim)

XM02 is the common formulated filgrastim for Biograstim, ratiograstim and tevagrastim. The formulation is the same as Neupogen, except it use different concentration of polysorbate 80 and different pH. This slight difference may account for hiher storage temperature of XM02 than that of Neupogen **(Table 2)**. The clinical efficacy is comparable to Neupogen in a way that XM02 leaded to same peak CD34+ cell counts at 72 hours and the CD34+ cell counts returned to base level after 336 hours, exactly the same time profile with Neupogen. The mean ANC levels were comparable too. XM02 does not induce immunogenicity as no antibody formation was identified. In pooled analysis of 3 studies, there were statistically more AEs in Neupogen-only group than XM02-only group but the author claimed that this is unlikely to be of clinical evidence.[37]

Table 2. Characteristics of various G-CSF agents

	Neupogen (reference product)	XM02	Zarzio/Hexal	Nivestim	Lenofilgrastim	Pegfilgrastim	Lipegfilgrastim
Active substance	Filgrastim	Filgrastim	Filgrastim	Filgrastim	Lenograstim	Pegfilgrastim	Lipegfilgrastim
Host system	*E. coli*	*E. coli*	*E. coli*	*E. coli*	Chinese Hamster Ovary cells	*E. coli*	*E. coli*
Protein characteristics	175 amino acid long; Non-glycosylated	175 amino acid long; Non-glycosylated	175 amino acid long; Non-glycosylated	175 amino acid long; Non-glycosylated	174 amino acid; glycosylated at Thr-133	pegylated filgrastim	pegylated filgrastim with carbonhydrate linker (covalent modification)
Buffer system	acetate	Acetate (but different pH from Neupogen)	glutamate	Acetate	Sodium phosphate	Acetate at pH4.0[26]	Acetate acid
Other excipients	Glacial, sodium hydroxide, sorbitol (E420), polysorbate 80, water	Glacial, sodium hydroxide, sorbitol (E420), polysorbate 80, water	Sorbitol (E420), polysorbate 80, water	Glacial, sodium hydroxide, sorbitol (E420), polysorbate 80, water	Human albumin, mannitol polysorbate 20, sodium chloride[36]	Sodium hydroxide, sorbitol (E420), polysorbate 20. water	Sodium hydroxide, glacial, sorbitol (E420), polysorbate 20. water
Shelf life	24 months at 2-8°C[38]	24 months at 5±3°C	24 months at 5±3°C	30 months at 2-8°C (480µg/0.5ml); 24 months at 2-8°C (120µg/0.5ml, 300µg/0.5ml)	24 months at room temperature	3 years at 2-8°C	2 years at 2-8°C

Zarzio/Hexal

The chemical composition of Zarzio/Hexal is the same as Neupogen but only the buffer systems are different: Zarzio/Hexal adopts glutamate whereas Neupogen adopts acetate. Zarzio/Hexal has the same time profiles of CD34+ cell count. However, the serum levels of free G-CSF lower after administration of Zarzio/Hexal than after administration of Neupogen. This discrepancy is statically consistent across the different administration routes and dosage. Zarzio/Hexal is bioequivalent to Neupogen in terms of the elimination half-life. It was concluded that Zarzio/Hexal and Neupogen are therapeutically comparable in efficacy and safety.[37]

Nivestim

Nivestim achieved therapeutic equivalence with Neupogen as it has the same primary endpoint ANC and AUC, mean ANC and CD34+ counts. It was said that it was not statistically significant given that it takes longer for patients suffering from severse neutropenia to recover ANC when Nivestim was administrated instead of Neupogen (Nivestim: 14.2%, n=26; Neupogen: 9.5%, n=9).[37]

CONCLUSION

Although preclinical and clinical studies showed the therapeutic comparability (or even equivalence) of biosimilars to Neupogen in terms of efficacy and safety. The authority should keep on doing pharmacovigilance to ensure the safety of the biosimilar filgrastim as there were still some statistically differences (but not clinically invalid) evidence showing incidence of adverse events associated with administration of some biosimilars, especially for those newly approved ones like Accofil and Gastophil.

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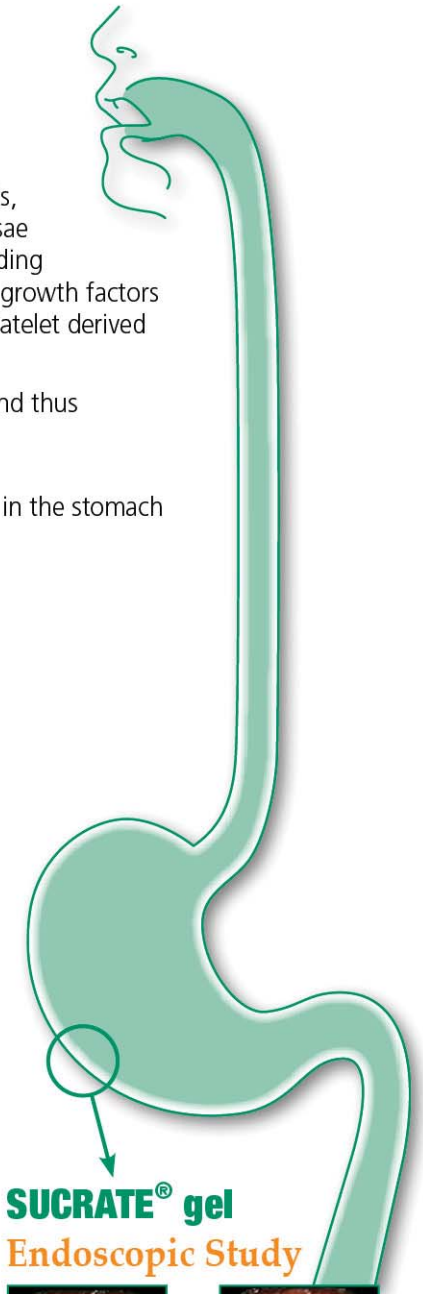

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Differences between Tufuling and Fuling Based on Their Chemical Constituents, Biological Effects and Medicinal Use

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ABSTRACT

The scientific name for Tufuling and Fuling is Smilax Glabra Rhizoma and Poria Cocos Sclerotia, respectively. Due to the similarity between these herbs, whether in their Chinese and English names or in their morphological appearance when sliced thin, it can be so hard to distinguish them from each other. Our survey reveals that the latter, instead of the former, has been used as one of the main ingredients in Gui-ling-gao in a few brands on the market since 2009. It is important to note, these two herbs are actually two different species and would give rise to different medicinal effects on the human body. This review article aims to differentiate the content of their bioactive components and medicinal uses based on what were reported in the literature. It is concluded that they should not be used interchangeable.

Keywords: *quality assurance, Gui-ling-gao, Turtle jelly, Tufuling, Fuling, Smilax Glabra Rhizoma, Poria Cocos Sclerotia, health food regulation*

INTRODUCTION

The scientific name for Tufuling (土茯苓) and Fuling (茯苓) is Smilax Glabra Rhizoma (SGR) and Poria Cocos Sclerotia (PCS), respectively.(1) These two herbs are very similar to each other in terms of their common names whether in Chinese or English and their morphology when sliced thin. It is worthwhile to mention them here due to it is found, in recent years at least, they have been used interchangeably in the popular Chinese health food or herbal "medicine" called Gui-ling-gao (龜苓膏).

Gui-ling-gao, also known as turtle or tortorise jelly, is a very popular traditional functional food in southern China. The history about Gui-ling-gao does vary and is really hard to validate these days since this herbal "medicine" or health food has been brought down as known for generations in China the great legacy as both health food and medicine for the whole world. Therefore there are quite a lot myths and legends about its origin and history. Here is the most popular one found from two different sources but similar story about Gui-ling-gao and its ingredients.(2,3)

One legend says that Gui-ling-gao comes from the county of Wuzhou (梧州) in Guangxi (廣西) province in China.(4) During the Era of the Three Kingdoms (AD 220-280) in ancient China, the famous Marshal, ZhuGe Liang (諸葛亮), led his troops down the south to Wuzhou. It was (and it is still) humid and extremely hot there in Wuzhou. At that time, most of his soldiers were from the north and were just suffering badly from the heat. Locals from Wuzhou then offered him and his soldiers this local remedy (Gui-ling-gao) comprising of turtle (or tortoise) shell fragments and herbal roots "Tufuling" (土伏苓, Smilax Glabra Rhizoma) for the heat stroke. They just recovered from the illness after taking this herbal "medicine", regained their strength and continued fighting the hard battle. Another story about the origin of Gui-ling-gao says that it was an extravagance food initially prepared for the Majesty of the Chinese Emperor and for the nobles during the Ham Fung Era of the Qing Dynasty in the 16th AD. The recipe of this jelly food was subsequently passed to a farmer to cure his skin problems in Guangdong through an imperial physician, YIN Yu-Man, after his retirement.

Gui-ling-gao is very popular nowadays amongst the Chinese and has become a big food business in southern China and oversea. Gui-ling-gao is so popular because it is claimed that it may be used to treat various ailments and health disorders by oral rout. It is believed that this jelly contains vital essences and could improve skin disorders such as spots or blemishes on the skin. It is also claimed to be hepatoprotective, antioxidative and can minimise the effects of damp-heat, nourish yin and promote urination and remove toxin from the body.(5,6)

Turtle shell and Smilax Glabra Rhizoma (SGR), which common name is Tufuling are the two main ingredients in Guiling Gao.(7) The jelly is made by stewing the turtle shell for about 20 h, and then the stew is added to a broth made from many herbs including SGR. The result is a bowl of steaming, quivering black goo.(8) However, as there is no definite herbal formula documented in literature except that plastron and a herb with a postfix character of "- ling" this broad-meaning postfix "-ling (苓)" could possibly be Tufuling (土茯苓), i.e. SGR or simply Fuling (茯苓), i.e PCS as one of those major ingredients. Individual manufacturers may have their unique formulae to massively produce their own herbal jelly, as our survey shows the ingredients used in different brands do vary. Therefore those end-products with different brands claiming they are gui-ling-gao may not even give the same effect on the same person, which is a big concern. In view of this inconsistent use of those two herbal ingredients, this review is in the hope of sharing and exchanging some basic but can be easily neglected background information with readers.

SURVEY OF INGREDIENTS IN GUI-LING-GAO PRODUCTS

Different brands of Gui-ling-gao were monitored or purchased between 2000 and 2015 from local stores, supermarkets and the franchised stores in both Hong Kong and Mainland China. Samples were then collected from these brands. Details of these samples are listed in **Table 1**.

Limitations for the Survey

It is worth to note that some samples, could not be taken from the same brand over the studying period for further comparison, except for a few brands. This could be due to various reasons such as the brand/product name was changed, the producers of those brands could not survive, etc.

Survey of Gui-ling-gao Products

Table 1 reveals that the samples collected from some popular brands of Gui-ling-gao bought before 2009 contain both turtle shell and SGR (Tufuling) as the main ingredients whether they were products of Hong Kong or Mainland China. However, this good practice was given up by most of the Gui-ling-gao producers even of the same brands when sampling was conducted since 2013. As shown in the table, it was found more than 50% of Gui-ling-gao samples had their two main ingredients, i.e. turtle shell and tufuling replaced by something else. The reason behind this sudden change is not known, but it can be obviously seen from the survey, 90% of the Gui-ling-gao samples collected from Mainland China had the turtle shell and Tufuling replaced by the starch and Fuling respectively since 2013. The survey shows the ingredients of the samples collected from Hong Kong have not changed much over time.

According to literature documents, it was surprisingly found that Fuling, not Tufuling was "recommended" in the quality control and safety requirements stated by the Guangxi government in 2009.[9] In order to compare and judge if this change of ingredients will work as fine, even further literature search on the chemical components and biological aspects of these two herbs have been conducted and which have been summarized in the following paragraphs.

TUFULING

Tufuling (*Smilax glabra* Roxb) is also known as guangyebaqia, glabrous greenbrier, the Chinaroot or sarsaparilla **(Figure 1, left plate)**.[10] There are about 300 species in the Smilax genus in the world, grown in the wild in tropical areas throughout the world. In the Himalaya region of China and in Indochina, only approximately 60 species have been identified. All of them belong to the Liliaceae family.

Tufuling (**Figure 1**, right plate), is the dried rhizome. It can be either *Smilax glabra* Roxb, *S. china, S. glauco-china Warb.*, *Heterosmilax japonica* Kunth, *H. chinesis* Wang, or *H. yunnanensis* Gagnep. All of them can be used as medicines by herbalists. Tufuling is subcylindrical, slightly flattened or irregularly strip-shaped, with knob-like outgrowths and short branches, 2-26 cm long, 20-80 mm in diameter. Externally the rhizome is yellowish-brown, uneven, with stiff remains of

Table 1. Details of collected samples of Gui-ling-gao.

Brand Code*	Product Name	Origin	Year of Survey	Ingredients+
AB-1	Turtle Jelly (original flavor)	Guangdong	2013	Starch, *Poria cocos*, Lonicerae Japonicae Flos, *Mesona chinesis*, etc.
AB-2	Turtle Jelly with Siraitia Grosvenorii	Guangdong	2013	Starch, *Poria cocos*, Lonicerae Japonicae Flos, *Mesona chinesis*, *Siraitia grosvenorii*, etc.
AB-3	Turtle Jelly (Orange flavour)	Guangdong	2013	Starch, *Poria cocos*, Lonicerae Japonicae Flos, *Mesona chinesis*, etc.
BC	Wuzhou Guilingao	Guangxi	2013	Starch, *Poria cocos*, Lonicerae Japonicae Flos, *Taraxacum mongolicum*, etc.
CY	Herbal Jelly	Hong Kong	2000, 2015	Turtle shell, SGR, etc.
DJ-1	Turtle Jelly	China	2008	Turtle shell, SGR, Lonicerae Japonicae Flos, Taraxaci Herba etc.
DJ-2	Tortoise Plastron Herbal Jelly	Shenzhen	2013	Testudinis Plastron, SGR, Lonicerae Japonicae Flos, *Mesona chinesis*, etc.
EF-1	Herbal Turtle Jelly	Hong Kong	2008, 2015	Turtle shell, SGR, Lonicerae Japonicae Flos, Rehmanniae Radix, etc.
EF-2	Herbal Turtle Jelly with Lingzhi	Hong Kong	2008, 2015	Turtle shell, SGR, Rehmanniae Radix, Abri Herba, Lingzhi, etc.
EF-3	Gi Gi Gui Ling Gow	Hong Kong	2015	Turtle shell, SGR, Lonicerae Japonicae Flos, Rehmanniae Radix, etc.
EL	PrimerTurtle Jelly	Hong Kong	2008	Turtle shell, SGR, etc.
FT-1	Traditional Fresh Herbal Jelly	Hong Kong	2008, 2015	Fresh turtle shell, Fresh SGR, Fresh Phragmitis Rhizoma, Lonicerae Japonicae Flos, Alpiniae Oxyphyllae Fructus, etc.
FT-2	Pearl Turtle Jelly	Hong Kong	2008	Turtle shell, SGR, Eucommiae Folium, Rehmanniae Radix, Pearl, etc.
FT-3	Fu Ling Gow	Hong Kong	2008	Fresh SGR, Plantaginis Herba, *Spina gleditsiae*, Aurantii Fructus, etc.
FT-4	Gui Ling Gow	China	2014	Gui Ling Gow, Poria Cocos Sclerotium, Testudinis, Trionyx sinenesis, Polygonati Rhizoma, Pueraniew Radix, etc
FT-5	Herbal Jelly	China	2015	Testudinis, Poria Cocos Sclerotium, Alpiniae Oxyphyliae Fructus, Chinese Yam Rhizoma, Phragmitis Rhizoma, etc.
GY	Chinese Herbal Jelly	Guangxi	2013	Starch, Poria Cocos, Lonicerae Japonicae Flos, *Taraxacum mongolicum*, etc.
HW-1	Emperor Turtle Jelly	Hong Kong	2008, 2014	Turtle shell, SGR, *Rheum rhabarbarum, Mesona chinesis*, etc.
HW-2	American Ginseng Turtle Jelly	Hong Kong	2008, 2014	Turtle shell, SGR, *Panax quinguefaliam, Panax ginseng, Mesona chinesis*, etc.
HW-3	Essence Turtle Jelly	Hong Kong	2008, 2014	Turtle shell, SGR, Rehmanniae Radix, Abri Herba, Lingzhi, Cervi Cornu Pantotrichum, etc.
JW	Kwei Ling Ko	Hong Kong	2004, 2008, 2015	Turtle shell, SGR, *Taraxacum mongolicum*, *Dictamnus dasycarpus*, *Forsythia suspensa*, etc.
KH-1	Turtle Jelly (original flavor)	Guangdong	2013	Starch, *Poria cocos*, Lonicerae Japonicae Flos, *Mesona chinesis*, etc.
KH-2	Turtle Jelly with Siraitia Grosvenorii	Guangdong	2013	Starch, *Poria cocos*, Lonicerae Japonicae Flos, *Mesona chinesis, Siraitia grosvenorii*, etc.
KH-3	Turtle Jelly (Orange flavour)	Guangdong	2013	Starch, *Poria cocos*, Lonicerae Japonicae Flos, *Mesona chinesis*, etc.
LQ	Turtle Jelly	China	2008	Turtle shell, SGR, Lonicerae Japonicae Flos, Mori Folium, etc,
MF-1	Golden Turtle Jelly	Hong Kong	2008	Turtle shell, SGR
MF-2	Herbal Jelly	Hong Kong	2013	Testudinis Plastron, SGR, Poria cocos, Abrus Cantoniensis Herba, *Mentha hapllocaly*, etc.
NY	Lingzhi Herbal Jelly	China	2014	Tortoise Shell, Poria, Lonicerae Japonicae Flos, Momordicae Fructus, Ganoderma lucidum, etc
PS	Turtle Jelly	Zhonshan	2000	Turtle shell, SGR, Rehmanniae Radix, Atractylodes Rhizoma etc
QW	Golden Herbal Jelly	Hong Kong	2013	Turtle shell, SGR, etc
RZ	Siphonage Guling Gao	Guangxi	2013	Tortorise shell, Lohankae, honeysuckle, Taraxacum, Poria, etc.

* The first two letters are arbitrarily assigned to represent a manufacturer, the digit represents product line.
\+ Based on manufacturer's claim in label or pamphlet.

Figure 1. *Photographs of a Smilax glabra Roxb plant (Left)[4] and its dried rhizome (Right).[5]*

fibrous roots, and with rounded bud scars at the top. Some outer bark are irregularly fissured and could be fallen off easily with scales left behind. Texture of the rhizome is hard but once fractures, it looks whitish to pale reddish-brown; and is starchy. On the surface of fracture, which is slightly tough, dusting on breaking, viscous and slippery when moistened, some dotted vascular bundles and numerous small light spots frequently distributed near the centre could be observed. The herb is odourless; slightly sweet and astringent if tasted.[11]

Chemical Constituents

Previous researches revealed that SGR contains lots of bioactive components. Chemicals which have been isolated and identified from SGR, include syringic acid,[12] ferulic acid,[13] taxifolin,[12,14] resveratrol,[15] astilbin,[12,13,15,16] smitilbin,[15] engeletin,[15] dihydroquercetin,[15] eurphin,[15] 5-O-caffeoylshikimic acid,[15] methylsuccinic acid,[12] smiglanin,[12,17,18] isoflavone,[12] O-(3)-caffeoylshikimic acid,[13] shikimic acid,[13] beta-sitosterol,[13] smiglabrin,[19] isoastilbin[17,20] and smiglasdie A-E.[21] Many of these bioactive compounds are dihydro-flavonol glycosides, such as astilbin, neoastilbin, isoastilbin and neoisoastilbin as well as smitilbin. The last component is a flavanonol rhamnoside. Besides, sarsasapogenin, a steroidal sapongenin, is also found in SGR. A study revealed that astilbin is the main constituent in the herb with contents ranging from 1-4%, while taxifolin is also present.[22]

Biological Effects and Functions

Astilbin is a dihydroflavonol rhamnoside with antioxidative,[23] antibacterial[24] and hepatoprotective activities.[25-28] Previous studies showed that astilbin could inhibit lymphocyte migration and suppress delayed-type hypersensitivity, negatively regulate the activity of cytokine and inhibit contact hypersensitivity.[29,30] It may also have significance in the treatment of immunologically related diseases.[31] Taxifolin is the aglycone of astilbin. Studies show that it can reduce cerebral ischemic reperfusion injury in rats through its antioxidative effect.[32] It can also up-regulate phase II detoxification enzymes through an antioxidant response element in HCT 116 cells.[33]

When astilbin was administered intravenously to mice demonstrating induced-pain by glacial acetic acid or contacted pain on hot plate, it provided analgesic effect or raised the pain threshold in mice.[34] This study demonstrated that astilbin has anti-nociceptive effects.

Using HepG2 cells as a model, Theriault et al demonstrated that taxifolin could decrease hepatic lipid synthesis with a concomitant decrease in apolipoprotein B.[35] Further research showed that taxifolin reduced apolipoprotein B secretion by limiting triglyceride availability.[36]

Medicinal Uses

The major application of this herb is to cleanse toxins and to reduce dampness. It is good for treating chronic and recurrent damp-heat skin disorders and acute skin lesions caused by heat. With the actions of clearing heat and removing toxins, it is good for curing sores, abscess and deep-rooted boils, swollen and sore throat, swelling and pain of gum. When this herb is combined with Lianqiao, and Pugongyin which are also specialized in removing toxins, it gives the best result.

In addition, Tufuling has been used to treat syphilis that is infected by the spirochete bacterium. The primary route of transmission is through sexual contact; it may also be transmitted from mother to fetus during pregnancy or at birth, resulting in congenital syphilis. The symptoms are diffuse rash which frequently involves the palms of the hands and soles of the feet. In a more serious case, gumma, neurological, or cardiac symptoms may be developed. To treat syphilis with Tufuling, decoction in large dosage has to be taken orally and/or combined with heat-clearing and toxicant-removing herbs such as Jinyinhua, Baixianpi, Viyiren and raw Gancao etc..

Tufuling can also be used for treating arthralgia. For anthralgic syndrome due to damp-heat, it is often used in combination with wind-damp-dispelling and heat-clearing herbs such as Qinjiao, Fangji and Luoshiteng, etc..

It was claimed that Tufuling is also good for treating gonorrheal urethritis, scabies, tinea, psoriasis, dysentery, ulcerative colitis and vaginitis.

FULING

Fuling, is also known as Indian bread, hoelen, tuckahoe or poris **(Figure 2)**,[37] All of these are dried sclerotium, including the reddish outer portion of the white fungus, *Poria cocos* (Schw.) Wolfs of the Polyporacease family. The sclerotium growing underground on the roots of pine and other trees are collected mostly in July to September and repeatedly dried under the sun until the outer skin turns

Figure 2. *Morphology of dried Poria cocos (Schw.) Wolf [37]*

Table 2. ummary of various features/differences between Tufuling and Fuling.

		Tufuling (土茯苓) aka Smilax Glabra Rhizoma	**Fuling** (茯苓) aka Poria Cocos Scierotia
Botanical Classification		Evergreen climbing shrub belonging to Liliacease family	Ball-like mushroom of Polyporacease family parasitically growing on the root of red pine or other conifers
Pharmacological Effects		Anti-inflammatory, anti-microbials, anti-cancer, inhibitory effect on HIV-1 reverse transcriptase	Immunomodulatory activity through activating macrophages, diuretic and cardiotonic
Bioactive Components		Astilbin, Taxifolin, trans-resveratrol, syringic acid, dihydrokaempferol	Pachyman (a polysaccharide), pachymic acid, tumulosic acid eburicoic acid, poricoic acid
Action	**Similarity**	remove excess dampness	cause diuresis to remove excess dampness,
	Differences	counteract toxicity of toxins or toxicants, to improve the mobility of joints	invigorate the spleen function, to calm the mind
Indications		Dysuria with turbid discharge, morbid leukorrhea, vaginal fungal infection, acne, carbuncle, lymphadenitis, chronic eczema, contracture of limbs and muscle pain in syphilis with mercury poisoning, carbuncles, scurvy, rheumatism	Edema with oliguria, dizziness and palpitation caused by retained fluid, diminished function of the spleen marked by anorexia, loose stools or diarrhea, restlessness and insomnia, obesity
Side Effects		No information available	Safe, possibly inhibits and activates MBL2 gene[61]
Interaction with Food and other Drugs		No information available	No information available
Purposes of Consumption		Tea, soup, medicinal uses for curing skin problem of old people, also a famine food,	Slimming herbal tea, or cake ingredients for tonifying the spleen and kidney
Medicinal Values		high	low
Regulatory Control in China		Required endorsement and registration number before use in health food	Less stringent; could be used to mix with other food ingredients without a registration number
Therapeutic Category		Anti-fabrile and anti-dotal, clearance of lead poisoning [62]	Diruetic, urination problems, diarrhea, stomach problems

winkled, lustrous and red. When Fuling is cut, the cross section should be white.

Poria cocos is the very common species in Asia, America and Oceania. In China, it is mainly distributed in provinces such as Jilin, Henan, Anhui, Zhejiang, Fujian, Hubei, Sichuan, Guizhou, Yunan, Guangxi, Guangdong and Taiwan.

Chemical Constituents

Chemical constituents found in Fuling are triterpenoid derivatives, polysaccharides, ergosterol, caprylic acid, undecanoic acid, lauric acid, dodecenoic acid, palmitic acid, dodecanoate, caprylate, and other elements.[38,39] Triterpenoids are mainly composed of pachymic acid, pachymic acid, tumulosic acid, eburicoic acid, dehydroeburicoic acid,[40-42] 3β-hydroxylanosta-7,9[11],24-TCMLIBien-21-oic acid, pachymic acid methyl ester, tumulosic acid methyl ester, polypenic acid C methyl ester, poricoic acids A, B, C, D, G, H, AM, DM and so on.[43] Polysaccharides are mainly β-pachyman, pachymaran,[44] and glucan H11.[45]

Medicinal Uses

Poria cocos fungus has long been used medicinally in China. It was first documented in *Shen Nong Ben Cao Jing (The Divine Husbandman's Classic of Materia Medica)* and subsequently mentioned in most of other ancient herbal medicine literature. Since ancient times the sclerotium of *Poria cocos* has been grounded into power for healthcare by consuming it on daily basis. It was consumed in the old days to promote urination, seep dampness, strengthen the spleen and quiet the heart.

Modern biological studies reveal that it possesses a wide spectrum of pharmacological activities, such as diuretic,[46] anti-oxidant,[47] anti-aging,[48] anti-tumor,[45,49-52] anti-bacterial,[53] nematicidal,[54,55] anti-inflammatory[56-58] and antihypertonic stress activities,[52] which could be explained by the presence of various triterpenes and polysaccharides.

COMPARISON OF THE MORPHOLOGY FOR EACH HERB WHEN SLIDED

As shown in **Figure 3**, these two different herbs really look alike to each other, when sliced thin. If they were shown separately, it is hard to tell which is Tufuling or Fuling without captions.

Figure 3. *Appearance of decoction pieces of Tufuling (left) and Fuling (right).*[60]

CONCLUSION

The use of botanical substances for making a medicated drink or functional food to cure ailments or maintain a good physical life has been the primary healthcare of the Chinese people for several thousand years. Various stages of development of such direct exploration of the environment for remedies prevail in the country, These practices have been proved working just fine over thousands of years although they have been changing and improving endlessly. We have still been trying to understand the mysteriously underlying mechanism behind them by using our latest scientific methods.

It is concluded in **Table 2** below, in which those various features of Tufuling (Smilax Glabra Rhizoma) have been summarised and contrast with those of Fuling (Poria Cocos Scierotim).

Author's background

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The Art and Science of Integrated Pharmacy Practice

The Organizing Committee of the 2016 Pharmacy Conference set out to develop a technical program around the theme of "The Art and Science of Integrated Pharmacy Practice." The key objectives were: (1) To inform pharmacists of the latest trend of drug development and pharmacy practice, (2) To inspire pharmacists and pharmaceutical scientists to harness scientific and technological advances to benefit the patient, and (3) To attract attendees from the Pacific Rim and create opportunities for them to network with the local pharmacists and pharmaceutical scientists. The overarching goal of the Conference is two-fold: (1) To capture the breathtaking advances in life sciences, material science, digital and telecommunication technology, and data management as drivers of change; and (2) To illustrate how these advances are working collaboratively to open doors for pharmacists to be entrepreneurial in serving the citizens in Hong Kong.

Thus, Day 1 of the Conference will feature presentations by experts and leaders in the disciplines destined to transform pharmacy practice in Hong Kong. Thus, Dr. Wai-lun Cheung, who is Director of Cluster Services in the Hospital Authority, will share with us the progress made in the public-private interface initiative piloted. Professor Bill Charman, a prominent pharmaceutical scientist and a thought leader in pharmacy education and practice who is Dean of the School of Pharmacy at Monash University, will share his insight on how advances in the sciences, engineering, and mobile digital communication will shine the spot light on unmet needs in patients, thereby prompting the development of entrepreneurial roles of pharmacists. Professor Stuart Schweitzer, an influential health economist at the UCLA Fielding School of Public Health, has conducted seminal research on drug pricing and how it can be influenced by medical insurance. He will offer his thoughts on the possible impact of both factors in healthcare financing in Hong Kong.

The fourth talk will be a success story on cancer therapeutics. Professor Anthony Chan, who also is the Chief Director of the CUHK Phase I Clinical Trial Center, will speak on the prospects as well as limitations of manipulating the patient's immune system to battle cancer. Immunotherapy is a very active, promising research area in clinical oncology today. The final presentation before the Conference Dinner will be on coaching by Mr. Charlie Lang. Mr. Lang is a highly sought after speaker on the importance of coaching in determining the quality and effectiveness of leadership. For those who are interested, he will conduct a workshop on the nuts and bolts of coaching in the morning of the second day.

Two concurrent sessions, one on lipid management and the other on emerging therapeutics will complete the program for the early morning of Day 2. The highlight of the lipid management session is the talk on PCSK9 inhibitors, two of which were approved by the FDA in August 2015 to lower plasma cholesterol in patients refractory to aggressive statin treatment. The other early morning session features the utility of next generation sequencing to select drugs for patient, recent developments of nanotechnology in drug delivery and targeting, and advances in the pharmacological and surgical intervention of advanced Parkinson's disease.

After the morning break, three parallel sessions were scheduled, focusing on new antimicrobials and antivirals, biosimilars, and examples of public-private ownership. Two of the three sessions will end in invited oral presentations by recent graduates of their graduation projects in the Master of Clinical Pharmacy program or the M.S. in Pharmaceutical Manufacturing and Quality program. Today's students are tomorrow's leaders. By engaging the students now is a worthwhile endeavor to ensure sustainability of the conference.

The grand finale of the Conference will be a plenary session on a proposed framework of the Pharmacy Council. It is understood that the draft would have been revised as per the comments collected over 2 months of administrative and public consultation. The goal is to submit a final draft to the Food and Heath Bureau for legislative action by July 1, 2015

Several changes were introduced during the organization phase of planning. We will highlight only those that the registrants of the meeting will see or experience. First, there will not be a printed program book. A pdf version will be available on the conference website for download and making hardcopies. Second, the abstracts will be published as a supplement of the *Hong Kong Pharmaceutical Journal*. Third, a mobile app has been commissioned. Attendees may find it convenient to create a schedule of activities during the conference, to navigate through the abstracts of posters or invited talks, and to rate the quality of the presentations virtually real-time.

For almost two decades, the Pharmacy Conference has been the forum where pharmacists across sectors, as well as non-pharmacists, come together for an intense 3-4 months to put their creative energies forward to produce a cohesive masterpiece that everyone can identify with. The generous support of the sponsors, several of whom year after year, is critical to sustaining excellence in the pharmacy conference. We sincerely appreciate your partnership. This year, your sponsorship enables us to invite 8 rising stars and superstars from Australia, the United Kingdom, and the United States to share their art of applying cutting edge science in meeting the unique therapeutic needs of patients. On behalf of the Organizing Committee, may I invite you to support the 2016 Hong Kong Pharmacy Conference (www.pharmacyconference.org) as either a registrant or a sponsor? The discounted registration applies if you register before December 15, 2015

I look forward to greeting you at the Conference on February 27-28, 2016.

Vincent H.L.Lee

Chairman, Organizing Committee

Hong Kong Pharmacy Conference 2016

The Society of Hospital Pharmacists (SHPHK) Office Bearers and Subject Officers 2015-2016:

Appointment of Office Bearers and Subject Officers

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

- The nucleotide polymerase inhibitor with pan-genotypic activity[1] and a high barrier to resistance[2]
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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.[3,4]

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

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SOFOSBUVIR
400 mg TABLETS
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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.

Reference: 1. Sovaldi Hong Kong Prescribing Information (EUJAN14HKFEB14). 2. Kris V Kowdley et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive 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.

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ADCETRIS®
(TAKEDA)

Prepared by Andy Lam and edited by Lucilla Leung

Active Ingredient:
Brentuximab vedotin, an antibody drug conjugate which delivers an antineoplastic agent used in the treatment of relapsed or refractory CD30+ Hodgkin lymphoma (HL) in adult patients.

Presentation:
Each vial contains 50 mg of brentuximab vedotin. After reconstitution, each ml contains 5 mg of brentuximab vedotin.

Pharmacological Properties:
Brentuximab vedotin is an antibody drug conjugate (ADC) that delivers an antineoplastic agent that results in apoptotic cell death selectively in CD30-expressing tumour cells. Nonclinical data suggest that the biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalisation of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, MMAE, is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest and results in apoptotic death of the CD30-expressing tumour cell.
Classical Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL) express CD30 as an antigen on the surface of their malignant cells. This expression is independent of disease stage, line of therapy or transplant status. These features make CD30 a target for therapeutic intervention. Because of the CD30-targeted mechanism of action brentuximab vedotin is able to overcome chemo-resistance as CD30 is consistently expressed in patients who are refractory to multi-agent chemotherapy, irrespective of prior transplant status. The CD30-targeted mechanism of action of brentuximab vedotin, the consistent expression of CD30 throughout the classical HL and sALCL disease and therapeutic spectrums and clinical evidence in two CD30-positive malignancies following multiple lines of treatment provide a biologic rationale for its use in patients with relapsed and refractory classical HL and sALCL with or without prior autologous stem cell transplant (ASCT). Contributions to the mechanism of action by other antibody associated functions have not been excluded.

Indications:
ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):
1. Following autologous stem cell transplant (ASCT) or
2. Following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

Important Limitations of Use
- Renal impairment

No studies in patients with renal impairment have been formally conducted. Data are not yet available from studies in patients with renal impairment. Patients with renal impairment should be monitored carefully.
- Hepatic impairment

No studies in patients with hepatic impairment have been formally conducted. Data are not yet available from studies in patients with hepatic impairment. Patients with hepatic impairment should be monitored carefully.
- Older patients

The safety and efficacy in older patients aged 65 and older have not been established. No data are available.
- Paediatric population

The safety and efficacy of children less than 18 years have not yet been established. No data are available.

Dosage and Administration:
Brentuximab vedotin should be administered under the supervision of a physician experienced in the use of anti-cancer agents.
The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.
If the patient's weight is more than 100 kg, the dose calculation should use 100 kg. The maximal recommended dose is 180 mg. Brentuximab vedotin must not be administered as an intravenous push or bolus. The drug should be administered through a dedicated intravenous line and it must not be mixed with other medicinal products.

Complete blood counts should be monitored prior to administration of each dose of this treatment
Patients should be monitored during and after infusion. Treatment should be continued until disease progression or unacceptable toxicity (see Precautions). Patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles (approximately 1 year).

<u>Instructions for reconstitution</u>
Each single use vial must be reconstituted with 10.5 ml of water for injections to a final concentration of 5 mg/ml.
1. Direct the stream toward the wall of the vial and not directly at the cake or powder.
2. Gently swirl the vial to aid dissolution. DO NOT SHAKE.
3. The reconstituted solution in the vial is a clear to slightly opalescent, colourless solution with a final pH of 6.6.
4. The reconstituted solution should be inspected visually for any foreign particulate matter and/or discoloration. In the event of either being observed, discard the medicinal product.

<u>Preparation of infusion solution</u>
The appropriate amount of reconstituted ADCETRIS must be withdrawn from the vial(s) and added to an infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection in order to achieve a final concentration of 0.4-1.2 mg/ml ADCETRIS. The recommended diluent volume is 150 ml. The already reconstituted ADCETRIS can also be diluted into 5% dextrose for injection or Lactated Ringer's for injection.
Gently invert the bag to mix the solution containing ADCETRIS.

DO NOT SHAKE.
ADCETRIS is for single use only. Any portion left in the vial, after withdrawal of the volume to be diluted, must be disposed of in accordance with local requirements.
Do not add other medicinal products to the prepared ADCETRIS infusion solution or intravenous infusion set. The infusion line should be flushed following administration with sodium chloride 9 mg/ml (0.9%) solution for injection, 5% dextrose for injection, or Lactated Ringer's for injection. Following dilution, infuse the ADCETRIS solution immediately at the recommended infusion rate. Total storage time of the solution from reconstitution to infusion should not exceed 24 hours.

Determining dosage amount and the total number of ADCETRIS vials needed:

$$\frac{\text{ADCETRIS dose}\left(\frac{\text{mg}}{\text{kg}}\right) \times \text{patientls body weight (kg)}}{\text{Reconstituted vial concertration}\left(\frac{5\text{mg}}{\text{ml}}\right)}$$

Total ADCETRIS dose (ml) to be further diluted =

$$\frac{\text{Total ADCETRIS dose (ml) to be administered}}{\text{Total volume per vial}\left(\frac{10\text{ml}}{\text{vial}}\right)}$$

Number of ADCETRIS vials needed =

Dosage adjustment

Neutropenia

If neutropenia develops during treatment it should be managed by dose delays. See Table 1 below for appropriate dosing recommendations.

Table 1. Dosing recommendations for neutropenia

Severity grade of neutropenia (signs and symptoms [abbreviated description of CTCAEa])	Modification of dose and schedule
Grade 1 (<LLN - 1500/mm^3 <LLN - 1.5 x 10^9/L) or Grade 2 (<1500 - 1000/mm^3 <1.5 – 1.0 x 10^9/L)	Continue with the same dose and schedule
Grade 3 (<1,000 - 500/mm^3 <1.0 - 0.5 x 10^9/L) or Grade 4 (<500/mm^3 <0.5 x 10^9/L)	Withhold dose until toxicity returns to ≤ Grade 2 or baseline then resume treatment at the same dose and scheduleb. Consider growth factor support (G-CSF or GM-CSF) in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia.

a. Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0; see Neutrophils/granulocytes; LLN= lower limit of normal
b. Patients who develop Grade 3 or Grade 4 lymphopenia may continue treatment without interruption.

Peripheral neuropathy

If peripheral sensory or motor neuropathy emerges or worsens during treatment, see Table 2 below for appropriate dosing recommendations.

Table 2. Dosing recommendations for new or worsening peripheral sensory or motor neuropathy

Severity of peripheral sensory or motor neuropathy (signs and symptoms [abbreviated description of CTCAEa])	Modification of dose and schedule
Grade 1 (paraesthesia and/or loss of reflexes with no loss of function)	Continue with the same dose and schedule
Grade 2 (interfering with function but not with activities of daily living) or Grade 3 (interfering with activities of daily living)	Withhold dose until toxicity returns to ≤ Grade 1 or baseline, then restart treatment at a reduced dose of 1.2 mg/kg every 3 weeks

a. Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0; see neuropathy: motor; neuropathy: sensory; and neuropathic pain.

Contraindications:

ADCETRIS is contraindicated in patients with hypersensitivity to brentuximab vedotin or to any of the excipients: Citric acid monohydrate, Sodium citrate dihydrate, α, α-Trehalose dihydrate, Polysorbate 80. Combined use of bleomycin and brentuximab vedotin causes pulmonary toxicity.

Precautions:

Progressive multifocal leukoencephalopathy

John Cunningham virus (JCV) reactivation resulting in progressive multifocal leukoencephalopathy (PML) and death can occur in brentuximab vedotin-treated patients. PML has been reported in patients who received this treatment after receiving multiple prior chemotherapy regimens. PML is a rare demyelinating disease of the central nervous system that results from reactivation of latent JCV and is often fatal. Patients should be closely monitored for new or worsening neurological, cognitive, or behavioural signs or symptoms, which may be suggestive of PML. Brentuximab vedotin dosing should be held for any suspected case of PML. Suggested evaluation of PML includes neurology consultation, gadolinium-enhanced magnetic resonance imaging of the brain and cerebrospinal fluid analysis for JCV DNA by polymerase chain reaction or a brain biopsy with evidence of JCV. A negative JCV PCR does not exclude PML. Additional follow up and evaluation may be warranted if no alternative diagnosis can be established. Brentuximab vedotin dosing should be permanently discontinued if a diagnosis of PML is confirmed. The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g., cognitive, neurological, or psychiatric symptoms).

Pancreatitis

Acute pancreatitis has been observed in patients treated with brentuximab vedotin. Fatal outcomes have been reported. Patients should be closely monitored for new or worsening abdominal pain, which may be suggestive of acute pancreatitis. Patient evaluation may include physical examination, laboratory evaluation for serum amylase and serum lipase, and abdominal imaging, such as ultrasound and other appropriate diagnostic measures. Brentuximab vedotin should be held for any suspected case of acute pancreatitis. Brentuximab vedotin should be discontinued if a diagnosis of acute pancreatitis is confirmed.

Pulmonary Toxicity

Cases of pulmonary toxicity have been reported in patients receiving brentuximab vedotin. Although a causal association with brentuximab vedotin has not been established, the risk

of pulmonary toxicity cannot be ruled out. In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnoea), a prompt diagnostic evaluation should be performed and patients should be treated appropriately.

Serious infections and opportunistic infections
Serious infections such as pneumonia, staphylococcal bacteraemia, sepsis/septic shock (including fatal outcomes) and herpes zoster, and opportunistic infections such as Pneumocystis jiroveci pneumonia and oral candidiasis have been reported in patients treated with brentuximab vedotin. Patients should be carefully monitored during treatment for the emergence of possible serious and opportunistic infections.

Infusion-related reactions
Immediate and delayed infusion-related reactions (IRR), as well as anaphylactic reactions, have been reported.
Patients should be carefully monitored during and after infusion. If an anaphylactic reaction occurs, administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical therapy should be administered.
If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include paracetamol, an antihistamine and a corticosteroid. Infusion-related reactions are more frequent and more severe in patients with antibodies to brentuximab vedotin

Tumour lysis syndrome
Tumour lysis syndrome (TLS) has been reported with brentuximab vedotin. Patients with rapidly proliferating tumour and high tumour burden are at risk of tumour lysis syndrome. These patients should be monitored closely and managed according to best medical practice. Management of TLS may include aggressive hydration, monitoring of renal function, correction of electrolyte abnormalities, anti-hyperuricaemic therapy, and supportive care.

Peripheral neuropathy
Brentuximab vedotin treatment may cause a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. Brentuximab vedotin-induced peripheral neuropathy is typically an effect of cumulative exposure to this medicinal product and is reversible in most cases. In the phase 2 population, at the time of last evaluation, the majority of patients (62%) had improvement or resolution of their peripheral neuropathy symptoms. For patients who reported peripheral neuropathy, brentuximab vedotin treatment discontinuation occurred in 9%, dose reductions were reported in 8%, and dose delays occurred in 13% of patients. Patients should be monitored for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paraesthesia, discomfort, a burning sensation, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay and a dose reduction of brentuximab vedotin or discontinuation of treatment.

Haematological toxicities
Grade 3 or Grade 4 anaemia, thrombocytopenia, and prolonged (≥ 1 week) Grade 3 or Grade 4 neutropenia can occur with brentuximab vedotin. Complete blood counts should be monitored prior to administration of each dose. If Grade 3 or Grade 4 neutropenia develops, refer to Table 1: Dosing recommendations for neutropenia.

Febrile neutropenia
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count <1.0 x 10^9/L, fever ≥ 38.5°C; ref CTCAE v3) has been reported with treatment with brentuximab vedotin. Complete blood counts should be monitored prior to administration of each dose of this treatment. Patients should be monitored closely for fever and managed according to best medical practice if febrile neutropenia develops.

Stevens-Johnson syndrome
Stevens-Johnson syndrome has been reported with brentuximab vedotin. If Stevens-Johnson syndrome occurs, treatment with brentuximab vedotin should be discontinued and appropriate medical therapy should be administered.

Hepatic function
Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been reported. Liver function should be routinely monitored in patients receiving brentuximab vedotin.

Hyperglycaemia
Hyperglycaemia has been reported during clinical trials in patients with an elevated Body Mass Index (BMI) with or without a history of diabetes mellitus. However, any patient who experiences an event of hyperglycaemia should have their serum glucose closely monitored. Anti-diabetic treatment should be administered as appropriate.

Renal and hepatic impairment
There is limited experience in patients with renal and hepatic impairment. Population pharmacokinetic (PK) analysis indicated that MMAE clearance might be affected by moderate and severe renal impairment, and by low serum albumin concentrations

Sodium content in excipients
This medicinal product contains a maximum of 2.1 mmol (or 47 mg) of sodium per dose. To be taken into consideration for patients on a controlled sodium diet.

Drug Interactions:
Interaction with CYP3A4 inhibitors, inducers and medicinal products metabolized through CYP3A4 route
Co-administration of brentuximab vedotin with ketoconazole, a strong CYP3A4 and P-gp inhibitor, increased the exposure to the antimicrotubule agent MMAE by approximately 73%, and did not alter the plasma exposure to brentuximab vedotin. Therefore, co-administration of brentuximab vedotin with strong CYP3A4 and P-gp inhibitors may increase the incidence of neutropenia. If neutropenia develops, refer to Table 1: Dosing recommendations for neutropenia.
Co-administration of brentuximab vedotin with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to brentuximab vedotin; however it reduced exposure to MMAE by approximately 31%.
Co-administration of midazolam, a CYP3A4 substrate, with brentuximab vedotin did not alter the metabolism of midazolam;

therefore brentuximab vedotin is not expected to alter the exposure to medicines that are metabolized by CYP3A4 enzymes.

Side Effects:
The safety profile of ADCETRIS is based on available clinical trial data, the Named Patient Program (NPP), and post-marketing experience to date. Frequencies of adverse reactions described below have been determined based on data generated from clinical studies. Within each System Organ Class, adverse reactions are listed under frequency categories of: 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); not known (cannot be estimated from the available data).

System organ class	Adverse reactions
Infections and infestations	
Very common:	Infection
Common:	Sepsis/septic shock, upper respiratory tract infection, herpes zoster, pneumonia
Uncommon:	Oral candidiasis, Pneumocystis jiroveci pneumonia, staphylococcal bacteraemia
Frequency not known:	Progressive multifocal leukoencephalopathy
Blood and lymphatic system disorders	
Very common:	Neutropenia
Common:	Anaemia, thrombocytopenia
Frequency not known:	Febrile neutropenia
Immune system disorders	
Frequency not known:	Anaphylactic reaction
Metabolism and nutrition disorders	
Common:	Hyperglycaemia
Uncommon:	Tumour lysis syndrome
Nervous system disorders	
Very common:	Peripheral sensory neuropathy
Common:	Peripheral motor neuropathy, dizziness, demyelinating polyneuropathy
Respiratory, thoracic and mediastinal disorders	
Common:	Cough, dyspnoea
Gastro-intestinal disorders	
Very common:	Diarrhoea, nausea, vomiting
Common:	Constipation
Uncommon:	Pancreatitis acute
Hepatobiliary disorders	
Common:	Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased
Skin and subcutaneous tissue disorders	
Very common:	Alopecia, pruritus
Common:	Rash
Uncommon:	Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	
Very common:	Myalgia
Common:	Arthralgia, back pain
General disorders and administration site conditions	
Very common:	Fatigue, pyrexia, infusion-related reactions
Common:	Chills

Forensic Classification:
P1S1S3

INVOKANA™
(Johnson & Johnson)

Prepared by Benny Yim and edited by Lucilla Leung

Active Ingredient:
Canagliflozin, used in the management of type 2 diabetes.

Presentation:
Each tablet of 100 mg contains 102 mg of CANAGLIFLOZIN, corresponding to 100 mg of CANAGLIFLOZIN (anhydrous).
Each tablet of 300 mg contains 306 mg of CANAGLIFLOZIN, corresponding to 300 mg of CANAGLIFLOZIN (anhydrous).

Pharmacological Properties:
Sodium-glucose co-transporter 2 (SGLT2), which is expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Being an inhibitor of SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RTG), and thereby increases urinary glucose excretion.

Indications:
INVOKANA (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Limitation of Use
INVOKANA is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Dosage and Administration:
Recommended Dosage
The recommended starting dose of INVOKANA (canagliflozin) is 100 mg once daily, taken before the first meal of the day. In patients tolerating INVOKANA 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control, the dose can be increased to 300 mg once daily
In patients with volume depletion, correcting this condition prior to initiation of INVOKANA is recommended.

Patient with Renal Impairment
No dose adjustment is needed in patients with mild renal impairment (eGFR of 60 mL/min/1.73 m^2 or greater).
The dose of INVOKANA is limited to 100 mg once daily in patients with moderate renal impairment with an eGFR of 45 to less than 60 mL/min/1.73 m^2.
INVOKANA should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m^2.
Assessment of renal function is recommended prior to initiation of INVOKANA therapy and periodically thereafter. INVOKANA should be discontinued when eGFR is persistently less than 45 mL/min/1.73 m^2.

Concomitant Use with UDP- Glucuronosyl Transferase (UGT) Enzyme Inducers
If an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA, consider

increasing the dosage to 300 mg once daily in patients currently tolerating INVOKANA 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control.

Contraindication:

INVOKANA is contraindicated in patients with:

- History of a serious hypersensitivity reaction to INVOKANA
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease or patients on dialysis.

Precautions:

Hypotension

INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA [for detail, please refer to full monograph] particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin- converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Impairment in Renal Function

INVOKANA increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.

Hyperkalemia

INVOKANA can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically after initiating INVOKANA in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Genital Mycotic Infections

INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. Monitor and treat appropriately.

Increases in Low-Density Lipoprotein (LDL-C)

Dose-related increases in LDL-C occur with INVOKANA. Monitor LDL-C and treat per standard of care after initiating INVOKANA.

Drug Interactions:

UGT Enzyme Inducers

Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control.

Digoxin

There was an increase in the AUC and mean peak drug concentration (Cmax) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

Side Effects:

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions From Pool of Four 26−Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Female genital mycotic infections†	3.2%	10.4%	11.4%
Urinary tract infections‡	4.0%	5.9%	4.3%
Increased urination§	0.8%	5.3%	4.6%
Male genital mycotic infections¶	0.6%	4.2%	3.7%
Vulvovaginal pruritus	0.0%	1.6%	3.0%
Thirst#	0.2%	2.8%	2.3%
Constipation	0.9%	1.8%	2.3%
Nausea	1.5%	2.2%	2.3%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=312), INVOKANA 100 mg (N=425), and INVOKANA 300 mg (N=430).

‡ Urinary tract infections include the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=334), INVOKANA 100 mg (N=408), and INVOKANA 300 mg (N=404).

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Forensic Classification:

P1S1S3

First-line treatment for chronic hepatitis B (CHB) in adults[1-3]

Viread®
tenofovir disoproxil fumarate 300 mg

- Potent and sustained viral suppression[5]
- 0% resistance detected through 8 years[4,5]
- Regression of fibrosis or cirrhosis[6]

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 ≥12 years of age and ≥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 coinfected 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.

References: 1. Lok ASF and McMahon BJ. Hepatology 2009;50:1-36 **2.** EASL. Journal of Hepatology 2012;57:167-185 **3.** Liaw YF et al. Hepatol Intl 2012;6:531-56 **4.** Corsa A et al. AASLD 2014. Poster #1707 **5.** Marcellin P et al. AASLD 2014. Poster #229 **6.** Marcellin P et al. The Lancet 2013;381(9865):468-475

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