HONG KONG PHARMACEUTICAL JOURNAL

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1. Nishida, Y., Yamashits, E., And Miki, W., Carotenoid Science, 11, 16-20(2007)
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INSTRUCTIONS FOR AUTHORS

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

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

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

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

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

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Greetings from the new Editor-in-Chief

It is a great honour and privilege for me to assume the responsibilities of Editor-in-Chief of *Hong Kong Pharmaceutical Journal (HKPJ)*, taking over the helm from Dr. Cheung Hon-Yeung.

It is no secret that the world of publication and information dissemination is swiftly changing. New demands and expectations from both authors and readers have encouraged shifting perspectives among editors and publishers. One of my goals as Editor-in-Chief is to ensure that *HKPJ* remains flexible in attending to this rapidly changing landscape while maintaining the standard of the Journal. As with all social developments, the use of electronic media is now a vital component. I look forward to exploring ways to further enhance the outreach and dissemination of our articles to a broader set of research communities by leveraging electronic media.

During our first editorial committee meeting, new ideas have been exchanged and discussed as *HKPJ* will need to continue further advancement. We hope to bring about gradual changes in the near future, but rest assured as any changes in the Journal will be carefully considered in the light of whether they meet the Journal's scope and aims, and the wishes of its readers and authors. HKPJ will continue to serve the common interests of members, authors and readers to meet the challenges ahead.

On behalf of the Journal, I thank Dr. Cheung Hon-Yeung for his hard work and achievements as Editor-in-Chief and look forward to his continued support, albeit in a less intensive form. I look forward to this role and welcome input from you, our readers and contributors to enhance the overall quality of the journal. Together with the erudite team of our editorial committee, I aim to build on Dr. Cheung's successes and help steer the Journal to the next level. *HKPJ* welcomes your manuscripts submission and witness a pleasant experience while working with our editorial staff.

May PS Lam
Editor-in-Chief
28 October 2018

Prepared by Howard Chan; Chiu Tsz Ching; Bryan Kan; Tommy Lee

FDA: Update of Warnings for Fluoroquinolones for Risks of Mental Health and Hypoglycemia

Date: July 10, 2018

The US Food and Drug Administration has stepped up its action to strengthen the warnings on fluoroquinolones about the risk of mental health and severe hypoglycaemia. The warnings are required to be consistent and cover all fluoroquinolones regardless of the route of administration.

Fluoroquinolones were commonly used in the past for urinary and respiratory tract infections because of their potency, simple dosing regimen and easy intravenous-to-oral switch. However, they are now reserved given the rising resistance and increasing documentation of severe side effects. Incidents of QT prolongation, tendon rupture, hepatotoxicity, CNS adverse effects and worsened myasthenia gravis have been reported.

Mental health side effects are already described in the Warnings and Precautions section of the drug labelling across fluoroquinolone class with some individual differences. FDA has requested such information to be listed separately from other CNS side effects and to be appeared consistently for all fluoroquinolones. These side effects include disturbance in attention, disorientation, agitation, nervousness, memory impairment and delirium.

Hypoglycaemic coma was discovered by FDA in recent review. Hence, hypoglycaemia will be included in the Blood Glucose Disturbance subsection of the labelling for all systemic fluoroquinolones.

In Hong Kong, there are 188 registered pharmaceutical products containing fluoroquinolones, which are available as oral preparations or injectables for human use. They are ciprofloxacin (81 products), levofloxacin (62), moxifloxacin (5), norfloxacin (7), ofloxacin (31), sparfloxacin (1) and prulifloxacin (1). Meanwhile, the Department of Health has not received any reports related to the mentioned adverse effects for fluoroquinolones.

Source: www.fda.gov

EMA Recommendations on restricting Use of Prostate Cancer Medicine Xofigo

Date: July 14, 2018

European Medicines Agency's (EMA) safety committee Pharmacovigilance Risk Assessment Committee (PRAC) has recommended restricting the use of Xofigo (radium-223 dichloride) to patients who have had two previous treatments for metastatic prostate cancer or who cannot receive other treatments.

These restrictions follow a review of data from a study suggesting that patients given Xofigo seemed to be at risk of dying earlier and had more fractures than patients given placebo (a dummy treatment). It is thought that Xofigo, which is taken up by the bone, accumulates at sites where the bone is already damaged, for example by osteoporosis or micro-fractures, increasing the risk of fracture. However, the reasons for a possible earlier death in this study are not fully understood. EMA recommended that patients should be carefully assessed for their risk of fractures before, during and after treatment. Preventive measures such as the use of bisphosphonates or denosumab as agents to increase bone strength should be considered before starting or resuming treatment with Xofigo.

To date, the Department of Health (DH) has not received any cases of adverse drug reaction related to Xofigo about death and fractures. Related news was previously issued by various overseas drug regulatory authorities and was posted on the Drug Office website since 2 Dec 2017, with the latest update posted on 10 Mar 2018. As the above PRAC's recommendation will now be sent to the Committee for Medicinal Products for Human Use (CHMP) for further endorsement, DH will remain vigilant on the development of the issue and safety update of the drug issued by other overseas drug regulatory authorities.

Source: www.drugoffice.gov.hk

First Targeted Treatment Approved for Relapsed/Refractory Acute Myeloid Leukemia due to IDH1 Mutation

Date: July 20, 2018

The FDA approved Tibsovo (ivosidenib) tablets for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) who have an IDH1 gene mutation. A companion diagnostic was also approved concurrently to detect IDH1 gene mutations.

Tibsovo, an isocitrate dehydrogenase-1 inhibitor, reduces the abnormal production of 2-hydroxyglutarate (2-HG), an oncometabolite that leads to malignant cell differentiation. The efficacy of Tibsovo was established in a single-arm trial of 174 adult patients with relapsed/refractory AML with an IDH1 mutation. With a median follow-up of 8.3 months, 32.8 percent of patients experienced complete remission (no evidence of disease and full recovery of blood counts after treatment) or complete remission with partial hematologic recovery (no evidence of disease and partial recovery of blood counts after treatment) for a median of 8.2 months.

Tibsovo carries a boxed warning for differentiation syndrome, which symptoms may include fever, dyspnea, acute respiratory distress, radiographic pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain, peripheral edema or hepatic, renal or multi-organ dysfunction. Common side effects of Tibsovo include fatigue, increase in white blood cells, joint pain, diarrhea, shortness of breath, swelling in the arms or legs, nausea, pain or sores in the mouth or throat, QT prolongation, rash, fever, cough and constipation. Women who are breastfeeding should not take Tibsovo because it may cause harm to a newborn baby.

Source: www.fda.gov

First Generic EpiPen Approved by FDA

Date: August 16, 2018

The United States Food and Drug Administration (FDA) recently approved the first generic version of EpiPen and EpiPen Jr, an auto-injector containing epinephrine for emergency anaphylaxis treatment. Other products approved by FDA under new drug applications include Adrenaclick and Auvi-Q, with the former also having 'authorized generic' versions marketed without brand name. In view of potential drug shortage, such action signifies the advanced access to safe, effective alternatives at a lower cost.

Anaphylaxis is a series of hypersensitivity reactions which could be triggered by various factors, for instance insect bites or stings, foods, medications and latex. Fatal symptoms include drastic drop in blood pressure and airway contraction, which requires immediate management. Epinephrine exerts its effect by relieving airway swelling and increasing venous blood flow, and its injection provides a rapid onset with short duration of action.

Two strengths manufactured by Teva Pharmaceuticals USA, 0.3mg and 0.15mg, gained approval for marketing. At present, two epinephrine auto-injection products are available in Hong Kong, with Hong Kong Registration Numbers of HK-34030 and HK-34029 respectively.

Epinephrine injection is given intramuscularly or subcutaneously for adults and paediatric patients who weigh more than 33 pounds. Common side effects including anxiety, palpitations, and respiratory difficulties. Epinephrine should not be injected into the vein, buttock, fingers, hands or feet; leg movement should be limited to minimize risk of injection-site injury.

Source: www.fda.gov

Drug Office: Update on NDMA-tainted Valsartan Products

Date: August 21, 2018

Valsartan alone, or in combination with hydrochlorothiazide, can be used for hypertension and heart failure. Unfortunately, N-nitrosodimethylamine (NDMA), a "probable human carcinogen", was found in valsartan as active pharmaceutical ingredient and final products.

Trace amounts of NDMA were detected in the valsartan Active Pharmaceutical Ingredient (API) manufactured by Zhejiang Huahai, Zhejiang Tianyu and Zhuhai Rundu in China and Hetero Labs Limited in India.

National health authorities are currently taking immediate actions, including recalling and terminating distribution of valsartan-containing products from Zhejiang Tianyu. Effects on patients and the cause of this incident are pending investigation. According to the U.S. FDA, the current theory of contamination "may be related to a change in the chemical reactions used during the manufacturing process".

In Hong Kong, there are 83 registered pharmaceutical products containing valsartan. The Department of Health (DH) has yet to receive any reports on adverse reactions related to this issue.

DH has repeatedly issued news related to the issue since July. It has contacted certificate holders of all registered valsartan products using valsartan API produced by the aforementioned manufacturers for follow-up and recalls. For API produced by Zhejiang Huahai, there are five affected products marketed in Hong Kong (with Hong Kong Registration Numbers of HK-61786, HK-61787, HK-61784, HK-61785 & HK-60794). DH had instructed certificate holders to recall all affected products from the market as a precautionary measure, and all recalls had been completed.

Patients who are taking the products above should not stop taking the medication, but to seek advice from their healthcare professionals as soon as possible for proper arrangements.

Source: www.drugoffice.gov.hk

FDA Warning on Severe Genital Infection with SGLT2 Inhibitors

Date: August 30, 2018

FDA noticed the public that rare and severe cases of infection of the genital area and surroundings have been reported with a class of type 2 diabetes medications called sodium-glucose cotransporter-2 (SGLT-2) inhibitor. This infection is called necrotizing fasciitis of the perineum, also known as Fournier's gangrene.

Fournier's gangrene is a life-threating bacterial infection of the tissue under the skin that surrounds muscles, nerves and blood vessels of the perineum. Having diabetes is a risk factor for developing Fournier's gangrene, however, this condition is still rare among diabetic patients. Over the past five years, FDA received 12 cases of Fournier's gangrene in patients taking SGLT2 inhibitors. In most cases, Fournier's gangrene developed within several months after starting an SGLT2 inhibitor. Patients should seek medical help immediately if they experience any symptoms of tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum. If such infection is suspected, start treatment immediately with broad-spectrum antibiotics and surgical debridement if necessary. Discontinue the SGLT2 inhibitor, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

To date, there are 17 registered pharmaceutical products containing SGLT2 inhibitors. The Department of Health has received 2 cases of adverse drug reaction related to canagliflozin, 3 cases related to dapagliflozin and 1 case related to empagliflozin, but these cases are not related to Fournier's gangrene. Considering the above FDA's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Source: www.drugoffice.gov.hk

Brexanolone Injection Effective as Novel Treatment in Post-partum Depression

Date: August 31, 2018

Post-partum depression is the most common complication of childbirth and is estimated to affect 10-20% of women who give birth worldwide. However, many women treated for post-partum depression with conventional antidepressant therapies, e.g. selective serotonin-reuptake inhibitors (SSRIs), failed to achieve adequate response or full remission of symptoms. Brexanolone injection, a positive allosteric modulator of γ-aminobutyric acid type A ($GABA_A$) receptors, was investigated for the treatment of moderate to severe post-partum depression.

Two double-blind, randomised, placebo-controlled, multicentre phase 3 trials were conducted from 2016 to 2017. Eligible women were aged 18 – 45 years, 6 months post-partum or less at screening, with post-partum depression and a qualifying 17-item Hamilton Rating Scale for Depression (HAM-D) score (≥26 for study 1; 20-25 for study 2). In Study 1, patients were randomly assigned to receive a single intravenous injection of either brexanolone 90 μg/kg/h (BRX90), brexanolone 60 μg/kg/h (BRX60) or matching placebo in a 1:1:1 ratio. In study 2, patients were randomly assigned to receive BRX90 or matching placebo in a 1:1 ratio. The primary efficacy endpoint was the change from baseline in the 17-item HAM-D score at 60 h.

In study 1, at 60 h, the least-squares (LS) mean reduction in HAM-D total score from baseline was 19.5 points in the BRX60 group and 17.7 points in the BRX90 group. The differences in mean reduction compared to placebo (14.0 points) were −5.5 points for the BRX60 group (95% CI −8.8 to −2.2, p = 0.0013) and −3.7 points for the BRX90 group (95% CI −6.9 to −0.5, p = 0.0252). In study 2, at 60 h, the LS mean reduction in HAM-D total score from baseline was 14.6 points in the BRX90 group compared with 12.1 points for the placebo group (difference −2.5 [95% CI −4.5 to −0.5], p = 0.0160).

Administration of brexanolone injection for post-partum depression resulted in significant and clinically meaningful reductions in HAMD-total score at 60 h compared to placebo, with rapid onset of action and durable treatment response during the study period.

Source: www.thelancet.com

Daily Dose of Aspirin Associated with Increased Mortality Amongst Healthy Elderly

Date: September 16, 2018

Aspirin, an anticoagulant commonly prescribed for stroke prevention, was reported to bear association with higher overall mortality amongst healthy elderly people aged 70 or above upon daily use, according to a primary analysis of Aspirin in Reducing Events in the Elderly (ASPREE) conducted across Australia and the United States of America.

In ASPREE, a randomized and placebo-controlled trial conducted from 2010 to 2014, elderly volunteers without cardiovascular disease, dementia or disability were assigned to receive either 100mg of enteric-coated aspirin or placebo in approximately 1:1 ratio. After receiving each death notification, a single disease was assigned as an underlying cause which was most likely to have initiated the pathway to death. Proximal cause was further determined through the event that immediately led to death, such as bleeding.

With 1052 deaths occurred in total throughout the investigation, the proportion taken by the treatment group was higher than that of placebo group (hazard ratio [HR], 1.14; 95% confidence interval [CI], 1.01 to 1.29). Amongst participants treated with aspirin, cancer was identified as the major contributor to higher mortality regardless of tumor locations, with elevated risk of cancer-related death when compared with placebo group (HR, 1.31; 95% CI, 1.10 to 1.56). No significant difference was observed in terms of the proximal cause of death. The exact effects brought by aspirin on cancer remains to be seen.

Source: www.nejm.org

A New Digital Era in Pharmacy - Interview with Peter Suen

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INTRODUCTION

Mr. Suen Yiu Chan, Peter (孫耀燦藥劑師), who is the Director and the Chief Pharmacist of ActivaCare Pharmacy in Hong Kong, was awarded the Royal Pharmaceutical Society Leadership in Pharmacy Award in 2013. Peter is the first Chinese winner of this award for his effort in reducing medication errors and improving the quality of care by managing the medication system of Care and Attention Homes, training the nursing staff and implementing a pilot national guideline. The Hong Kong Pharmaceutical Journal, in recognition of his sustained progress and achievement over the past 10 years in advancing the pharmaceutical care of the old age homes elderly, has cordially invited him to an interview to share his project and vision with us.

Figure 1. *Mr. Suen was awareded the Royal Pharmaceutical Soceity Leadership in Pharmacy Award in 2013*

THE INTERVIEW

S: Mr. Suen
I: Interviewers

I: Pleased to meet you, Mr. Suen. As we know that you finished your Pharmacy degree in the United Kingdom, why did you come back to Hong Kong after graduation?

S: After getting the pharmacist registration certificate in the United Kingdom (UK), I have worked as a locum in a community pharmacy. Meanwhile, I continued with the postgraduate study in clinical pharmacy during my pre-registration training and further pursued my study with a law degree. Unfortunately, I failed to renew my Visa for continuing my stay in the UK. So, I dropped the law degree and went to Australia to visit my brother. With a short stay visa of 3 months validity, I took the Australian Pharmacy Law exam and a one-month pharmacy externship experience in order to get the Australian Pharmacist licence. After that, I returned to Hong Kong to develop my career.

I: We heard that you have a quite fascinating career. Could you tell us more about it?

S: Back then, there were only 100-200 community pharmacies in Hong Kong. With the poor flow of information, it was difficult to get a job. Friends were usually the only channel to obtain any news in the job market. To find a job for a living, I visited numerous community pharmacies in person. Luckily, a pharmacist working in the Yau Tsim Mong district had resigned and I successfully applied for the position. After working there for one week, I made up my mind to apply for an emmigration to Australia owing to the tremendous difference between the roles of community pharmacists in Hong Kong and the UK and Australia. Rather than providing proper pharmaceutical care to the patient, my job was to prepare drug records in Hong Kong, which made me unsatisfied with my working experience and discouraged me from further pursuing my career here.

After I moved to Australia, I continued to work as a community pharmacist and set up my proprietary pharmacy 2 years later. The professional experience in Australia is indeed rewarding. And my community pharmacy business was on a good track. However, life was dull outside of work so I decided to go back to Hong Kong again in 1989.

Because of the working experience in community pharmacy during my first return, I understood the importance of personal control of a pharmacy. I set up

my proprietary pharmacy in Mong Kok. Even though I encountered different difficulties and discouragement from others when I started my business, I persisted with hard work. It was an extremely difficult time and I didn't take a rest for more than 1 year. Eventually, my hard work paid off and I had set up a total of 12 pharmacies by 1999.

Since I easily got bored and the unprofessional working culture of the pharmacy staff made the pharmacy business more difficult, I gradually closed down all 12 pharmacies. Instead, by cooperating with my friends, I started the business in physician medical service in 2000 and a total of 12 clinics have been set up in 7 years. Until 2007, upon my friend request to be a locum in a pharmacy, I found myself forgetting to renew the annual practising certificate of pharmacists due to some technical problems. Fortunately, I could renew the practising certificate after contacting the Board and my business started to cover both pharmacy and physician medical service. Since 2008, I have invested around 30 million dollars in the medication management program, RightMed® Weekly Monitored Dosage System, in order to promote geriatric healthcare in Hong Kong. My career path was full of ups and downs, but I believed that "what is worth doing is worth doing well".

I: Why did you focus on the pharmaceutical services in old age homes?

S: It had to trace back to 1999. I visited a number of old age homes to observe their drug distribution systems as instructed by The Pharmaceutical Society of Hong Kong (PSHK) and discovered the underlying safety concerns of the inappropriate drug management. As most of the staff were unqualified and had low drug awareness, they made various mistakes frequently when they were carrying out their dispensing duties. Unfortunately, unless severe adverse drug reactions happened, a majority of medication errors were unnoticed and unreported. Worse still, the records of the distribution systems were mostly inaccurate and there was no way to trace back the staff member who made the mistake during the dispensing process for further follow-up actions. Without doubt, this approach of managing the drugs in elderly home was a blind alley if no improvement were to be made.

I: What have you done to improve the poor drug management system in old age homes after the visit?

S: By visiting the old age homes in Australia, I tried to introduce their drug management strategies into the old age homes in Hong Kong. To put the foreign practice through trials, a few pharmacists and I worked part-time for around 2 to 3 hours every day to make a tailored 7 days (7x4) pre-packed medication boxes for the old age homes in Hong Kong. We have spent about 6 months to finish all the 7x4 pre-packed medication boxes for one elderly home and another 3 to 4 months to expand the project to 2 more elderly homes. It was challenging to convince the staff in old age homes to acknowledge and appreciate our work because our work was making a cultural change to their working practice. The introduction of 7x4 pre-packed medication boxes received good responses from the old age homes and our work was fully supported by the management team of the old age home. In order to promote the project, the old age homes got a funding of 6 million dollars from the government to establish an in-house pharmacy and to employ their in-house pharmacists and dispensers for the daily operation. The elderly home of Chi Lin Nunnery (志蓮淨苑) was the first participant of this in-house pharmacy project in 1999.

I: What motivated you to come up with the idea of developing the dispensing service to the elderly home and the development of award-winning program?

S: When I renewed my practising certificate in 2008, I was informed that there were insufficient pharmacists in the in-house pharmacy of Chi Lin Nunnery's elderly home as a consequence of the limited supply of pharmacists in Hong Kong and the heavy workload of the in-house pharmacy. The in-house pharmacy was first established with a pharmacist and 4 dispensers of them only 2 dispensers stayed in their position at that time. So, I helped to take up the post of pharmacist for a while.

After working in the in-house pharmacy of Chi Lin Nunnery's elderly home for 2 months, I found that setting up in-house pharmacy in old age home was not a sustainable solution in consideration of the inadequate supply of pharmacists and dispensers in Hong Kong. To resolve the situation in the long term, I suggested a switch of dispensing service from the in-house pharmacy in old age home to the community pharmacy. And I have developed RightMed® Weekly Monitored Dosage System and conducted a pilot trial in my community pharmacy. The scheme was well received and there were an increasing number of old age homes joining the program. Yet, the increase in demand gradually overloads the dispensing capacity of my community pharmacy. In regard of this, a medication management centre located in Fo Tan was set up to expand the pharmacy ad dispensing service.

However, even the need of secondary dispensing is minimized, medication errors still existed when RightMed@ were given to the wrong patients by the untrained staff in the old age homes, revealing that the

workflow in the old age homes still posed a threat to the medication safety. The middle-aged women or new-immigrants, who were the major workforce of the elderly homes, were generally undertrained and error-prone. In addition, the low salary and insufficient manpower in old age homes gave rise to the frequent changes in personnel, further escalating the risk of medication errors, such as elderly misidentification. Hence, I was motivated to promote the IT applications in medication management at old age homes by developing eDrugAdmin@ and RMHome@ software based on the iOS system so as to reduce medication errors in old age homes. With the matched funding from The Trade and Industry Department, a total of more than 3 million dollars have been spent to implement the pilot scheme.

Figure 2. *Mr. Suen implemented the The RightMed® Weekly Monitored Dosage System in an old aged home*

I: What is the award-winning program about?

S: The program is about the RightMed® Weekly Monitored Dosage System, and the application of iOS-based eDrugAdmin® and RMHome®. The drug management centre first collects the drugs from the elderly homes. Dispensing services, including prescription review, medical reconciliation, dispensing and drug checking, are then held in the centre by the pharmacists and dispensers, in order to prepare a 7x4 pre-packed medication boxes for the elderly. When giving the drugs to the elderly, Radio Frequency Identification (RFID) technique is used to read the wristband of the elderly and the information is shown on the IOS-based software on iPad, which includes an enlarged photo of the elderly, anti-diabetic drugs warning, loud voice reminder, and electronic signature. The award-winning program has achieved a great drop of reported medication errors.

Figure 3. *The nurse uses The RightMed® Weekly Monitored Dosage System when dispensing drugs to patients*

I: What are the major difficulties in delivering this program to institutions? Any implication to policy/ service providers/innovators?

S: The government inspection team from Social Welfare Department (SWD) has called a halt to the program after it has been running for around 6 months. As regulated by the guideline from the SWD, old age homes are neither permitted to outsource drug handling process nor to use the 7x4 pre-packed medication boxes. A warning letter will be issued to old age homes if they continue with the practice. As a result, old age homes were forced to suspend the implementation of RightMed®. In order to convince the government for the allowance of the program, a lot of researches, investigations and discussions have been held to demonstrate the appropriateness of using a 7x4 pre-packed medication boxes in the Hong Kong old age homes context. Additionally, we proved the safety and quality of RightMed® by complying with the tailored-made local guideline. Eventually, the program could move ahead, and later, the government has changed the guideline to allow the use of 7x4 pre-packed medication boxes in Hong Kong.

Unfortunately, the program encountered another suspension for a while since the use of electronic signature was found to violate the SWD guideline. After a series of communication with the government, the guideline was modified again to permit the staff in old age homes to make records using any means, including the electronic signature. To some extent, I think that the political issues are one of the main resistance on our way to promote geriatric healthcare. Sometimes, government policy and guidelines are not catching up with the era. The bureaucracy provided extra hurdles for any innovative solution to be implemented in publicly funded institutions. For example, they don't understand the benefit of "RightMed® Weekly Monitored Dosage System" at first and are quite skeptical about the scheme. Also, it is difficult to encourage all the institutions, particularly non-NGO funded institutions, to contract their drug management out since it will increase their operation costs and unmask their Problems in drug management.

I: I know that you were awarded the Royal Pharmaceutical Society Leadership in Pharmacy Award in 2013. How did you feel when you received the award?

S: Since no Chinese have been awarded the Royal Pharmaceutical Society Leadership in Pharmacy Award before, I was very surprised when I heard my name being called in the ceremony. In my opinion, the prize was a recognition of my work in promoting geriatric healthcare. Royal Pharmaceutical Society is

a prestigious society in the field and industry. It was an uphill battle, with a lot of outstanding candidates from the UK competing for the award as well. To me, it is a great compliment that my work is appreciated at an international level.

Figure 4. *Mr. Peter Suen with Prof. Ian Wong in the ceremony*

I: RightMed® has been running for a few years since its implementation. How is the response of this program? Is it financially sustainable?

S: RightMed@ has been running for about 9 years and the number of beds in old age homes increases from 300 to more than 5000 now. Despite the annual price increase due to the elevating operation cost, the retention rate of the program still remains at 95%, revealing that the RightMed® is well received by the customers. We have recently achieved a great operational profit from this model, which indicates that this business model is viable and can be expanded to more old age homes. Therefore, we have introduced this service to different Care and Attention Homes, including physically handicapped persons and mentally handicapped persons.

I: The program is highly recognised by others. Will you further expand this service to other care/nursing home at a faster pace?

S: There are quite a number of Care and Attention Homes expressing their interest in our service, however, we set a quota for the expansion, which limits to one new Care and Attention Home each month. The major reason and difficulty that limits the expansion are the inadequate manpower resources, which has suspended the program for a few times.

The first time to call a halt to the expansion of the project in view of the inadequate manpower and complicated logistics in 2013. First, there was a shortage of pharmacists due to the escalating number of community pharmacies. Even with an increase of $10000 in the monthly salary, some of the pharmacists still resigned in the interest of the more attractive salary package offered by community pharmacies. Moreover, compared to the foreign graduates, local graduates have much fewer and limited dispensing experience as a result of the low prescription volume and training in the community pharmacy during their study and internship. Local fresh graduates might not have as much experience as their foreign counterpart.

Second, the supply of dispensers experienced in pharmacy practice could not meet the increasing demand. IVE is the only recognised institution to provide training for dispensers in Hong Kong at that time. The course content is focused on pharmaceutical production rather than pharmacy practice. In regard of this, the dispensers had to receive more specialized in-house training in our centre, but they might leave the work soon after they are qualified to provide dispensing service.

Third, since the drugs were provided by the hospitals rather than the nearby community pharmacy, numerous problems existed with the logistics. For instance, the drugs had to be collected from different hospitals at different time by the old age home. Also, the staff in old age home may keep some drugs with them, leading to the inaccurate amount of drugs collected by the medication management centre.

I: How did you meet the increasing demand for service?

S: In order to meet the increasing demand, the medication management centre has spent 1 year to get the certificate for all the procedures from the International Organization for Standardization (ISO), lessening the professional work of the pharmacists. When the number of beds in old age homes increased to about 4000, the program had to stop expanding due to the insufficient working area. In response to this, the working area was expanded gradually, and the potential use of automation was considered.

Unfortunately, the automated dispensing machines used in foreign countries didn't fit the situation in Hong Kong. First, there is no Chinese word on the machines, which poses a hindrance in the understanding of the staff in old age homes who may not be well-educated. Moreover, the dispensing system in Hong Kong is different from the foreign countries since there is no separation of dispensing and prescribing in Hong Kong. Hence it is difficult to apply the same dispensing model to the situation in Hong Kong. Another hurdle that we encounter is that about 60% of the prescriptions in Hong Kong contain items that are not dispensed in their unit dosage form but in half or quarter tablet. This implies that further procedures are needed for half or quarter tablets

and the manpower is not reduced despite the use of the dispensing machine.

Since the automation dispensing machines manufactured in foreign countries could not be directly introduced into Hong Kong, I had to find engineers myself to set up the own dispensing robot for Hong Kong, without using any funding, hoping to have a more flexible control of the time frame. Until now, around 30 million has been invested in the program and the automation robot has been running for 3 years.

I: Is there any insight that can be drawn from this program to the elderly care in Hong Kong?

S: I think the implementation of this program highlights certain difficulties of innovation under the inadequate labour supply and increasing operational cost. Even though there are many pharmacists unemployed recently, most of them are unwilling to join our team. Employing workers, especially young people, are getting more difficult in Hong Kong. Rent is getting up and the number of elderly will surge from 1.2 million to 3 million in the next 15 to 20 years. All these mean that automation is the only way out.


HEALTH

Tablet app ensures seniors get right medicine

Elderly patients linked to their pills via iPad

Figure 5. *The RightMed® Weekly Monitored Dosage System on Newspaper*

I: The service has been running for a while now and has been encouraged by your receiving of the award and the subscription to the service by the elderly care homes. What might be the possible future development that you can share with us?

S: In the future, it is more likely to set up the automation dispensing machine in the community pharmacy and run as a franchisee rather than running the whole program in the drug management centre. It can save the manpower and the logistic time. If the ratio of pharmacists to elderly increases to the standard of 1:1000, the community requires more than hundreds of pharmacists to run for franchisees. I do not believe the drug management centre can further develop, but the program will be developed in the community pharmacies. In the future, it is difficult to maintain individual business because franchisee is a more common business model due to lower operation cost and convenience. There are a lot of advantages to develop community-based dispensing service. For example, the transport time can be shortened, fewer drivers are needed at a shortage of working population, the saving of rent, and the reduction of renovation and maintenance cost. The mature business model of franchisee can attract people to invest on the machines for dispensing service. Indeed, it is also a potential way for the pharmacists to earn a living. If this program can be a component for the pharmacists and community pharmacies, this might facilitate the transition of the roles of local pharmacies from "poison-sellers" to pharmaceutical service providers.

Figure 6. *Automation Dispensing Machine*

I: We know that your service focuses on elderly medication safety. As we all know that Hong Kong is aging, with the elderly population doubles within the next 15-20 years. What are your thoughts on that? Is there anything that the pharmacy industry could take up in this era?

S: There are a lot of people working in this field. Some pharmacists advocate the notion of drug education in the elderly care context. In fact, I do not agree that drug education is the way of development in the future because it is not an easy job to convince the public to pay for the drug education or counselling. The storm of arguments over the flu vaccine recently reflected that scientific knowledge could easily be distorted by the rumours. This shows that merely advocating drug education is not as easy as we believe. Instead, expanding the dispensing service is a more effective way to reduce medication errors and to improve the quality of life of elderly. This year, PSHK has run a pilot scheme to promote RightMed@ to the elderly in the community other than those living in the elderly homes. Even though the government promotes home-based care service for the aging population, it is difficult to increase the drug awareness of the elderly. So, the effectiveness of the

pilot scheme can be analysed to explore the potential of RightMed@ to elderly with home-based care.

I: What do you think the most urgent/biggest issue for the pharmacy development/pharmaceutical care in Hong Kong in general right now?

S: The high unemployment rate of fresh graduates and the low passing rate of the registration exams are a matter of great concern. Contrary to their expectation of serving the patients and earning a living after their graduation, most of the pharmacy graduates fail to land on a hospital or government position. Graduates' interest in developing their career outside hospitals and government has certainly been hindered by the lack of respect in community pharmacies. In foreign countries, pharmacists have a high reputation in the society and their reputation is neither established by pharmacists working in hospitals nor pharmacists in government, but by the effort of the community pharmacists, who are the most easily approachable frontline healthcare persons. Community pharmacists provide good advice to the patients and solve minor illnesses for them, providing them with comfort. "Ask the pharmacists first. You will get the good advice" is a common belief in foreign countries, reflecting that medications only contribute to a portion of the recovery, and the rest comes from the confidence towards the pharmacists. In fact, around 80% Admission and Emergency (A&E) cases in Hong Kong could be handled by community pharmacists, but the general public has low awareness of seeking medical advice from their community pharmacists.

The root of the problem in Hong Kong is that there is no leadership in the pharmacy industry. The major responsibility of the government department is management and regulation, while that of the hospitals is providing dispensing service. Pharmacists working in these sectors only fulfill their responsibilities and there is lack of collaboration between different pharmacy sectors. Consequently, the current business model, policy environment and practice of community pharmacies in Hong Kong do not allow the majority of community pharmacists to get sufficient job satisfaction.

I: What do you think the young pharmacists should do/focus on to advocate pharmaceutical care in Hong Kong, given the fact that half of the graduates could not find clinical positions. Are there better ways for the industry to utilize this manpower?

S: In recent decades, the rapid social and economic development has changed the living environment and the value of the young generation, who possess more freedom when planning their career pathways. Rather than earning a living, job satisfaction becomes their major consideration. There has been an upward trend in continuing postgraduate studies if the graduate work is not their cup of tea. A lot of graduates wait for their dream jobs, especially for hospital pharmacists and government positions.

Meanwhile, some pharmacists spare their efforts on the home visit to promote the pharmacy profession, which I appreciate a lot. This would be fine if you do it with the intention of helping the underprivileged and acting out of benevolence. But if you aim to build the future and promote a sustainable development of pharmacy profession, home visit is a wrong battlefield for your war. The real place where the profession should shine is in the community.

However, community pharmacy is not respected by the public currently and has been a frustration to the young pharmacists in Hong Kong. As in foreign countries, community pharmacist is regarded as a clinical position and people there are willing to pay for medication reconciliation. Gaining reputation through community pharmacy is the only way to promote the profession. Some may say that separation of dispensing and prescribing can expand the job market and accommodate an increasing number of pharmacy graduates. Nevertheless, it won't take place unless there are massive changes to the current healthcare policies that shift the demand and supply of primary care such as the implementation of mandatory health insurance. The separation of dispensing and prescribing would be a big and uphill battle for pharmacists to fight for and would require a lot of prerequisites to become reality.

I: Thank you very much, Mr. Suen, for sparing your precious time to share the RightMed@ and your vision with us. Your hard work in improving medication safety in Care and Attention Homes was inspiring and enlightening to us. May we wish you every success in the promotion of RightMed@ and your future endeavours.

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Management Approach of Hemophilia A and B

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ABSTRACT

Hemophilia A and B are bleeding disorders caused by the deficiency of clotting factor VIII and IX respectively. Characteristic symptoms of hemophilia vary with severity. Patients with severe hemophilia may experience spontaneous bleeding, which could be life-threatening. Comprehensive care and routine health maintenance is essential to reduce the risk of bleeding in hemophilia patients. The optimal management approach of patients with hemophilia is complex and the development of neutralizing inhibitors becomes one of the biggest challenges. Treatment options should be individualized with multiple consideration factors, including inhibitor status, severity of disease and patient's response. With the introduction of new pharmaceutical products on the market and many other therapies under developmental stage, the management approach of hemophilia is ever evolving. This article will provide an overview of the background and management approach of hemophilia and outline the hemostatic agents used for hemophilia management.

Keywords: *Hemophilia, Hemophilia A, Hemophilia B, Clotting factor deficiency, Hemostatic agents*

INTRODUCTION

Hemophilia is an X-linked, recessive bleeding disorder caused by deficiency of functional plasma clotting factors associated with genetic mutation. Hemophilia A is caused by a deficiency of clotting factor VIII while hemophilia B results from a deficiency of factor IX.[1] The estimated frequency of hemophilia is one in 10,000 births, with an increasing trend in recent years.[1,2] Hemophilia A is more common than hemophilia B and represents 80-85% of the total hemophilia population.[3] Accurate diagnosis of hemophilia is essential to inform proper treatment. Appropriate therapy is of utmost importance as improper management of hemophilia could be life-threatening. Apart from traditional hemostatic agents, new therapies have been developed for the management of hemophilia. This article will review the background and the routine management approach of hemophilia A and B.

PATHOPHYSIOLOGY

The coagulation cascade **(Figure 1)** is a phase in hemostasis to propagate the blood clotting process. It involves the sequential activation of a series of proenzymes or inactive precursor protein zymogens into active enzymes, leading to the stepwise response amplification and blood clot formation.[4,5] The coagulation cascade is depicted as consisting the intrinsic and extrinsic pathway. The intrinsic pathway is initiated by exposure to negatively charged surface while extrinsic pathway is activated by exposure to tissue factor. Both pathways converge on the activation of factor X, which then activates prothrombin into thrombin and fibrinogen into fibrin, leading to the final clot formation.[6-8]

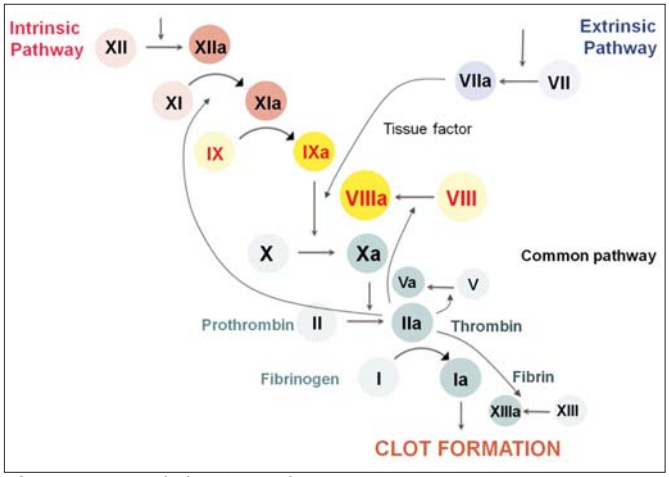

Figure 1. *Coagulation Cascade*

Factor VIII and factor IX are essential clotting factors in the coagulation cascade. Upon initiation of the coagulation cascade, factor IX and factor VIII activate into factor IXa and factor VIIIa respectively. Factor VIIIa brings together factor IXa and factor X to activate factor X for thrombin and fibrin generation.[9-11] As patients with hemophilia have deficiency in factor VIII or factor

Table 1. Severity of bleeding in hemophilia[1,3]		
Severity	**Clotting factor level**	**Bleeding Episodes**
Severe	< 1 IU/dl (<0.01 IU/ml) or <1% of normal hemostatic challenge.	Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable
Moderate	1-5 IU/dl (0.01 -0.05 IU/ml) or 1-5% of normal	Occasional spontaneous bleeding. Prolonged bleeding with minor trauma or surgery.
Mild	5-40 IU/dl (0.05-0.40 IU/ml) or 5-<40% of normal	Severe bleeding with major trauma or surgery. Spontaneous bleeding is rare.

Table 2. Site and approximate frequency of bleeding in hemophilia[1,14]			
Severity	**Site**	**Frequency**	**Remarks**
Life-threatening	Central Nervous System/ Head trauma	<5%	Least common but most life-threatening type of bleed. May lead to neurological damage.
	Neck / throat	5-10%	May lead to airway obstruction.
	Gastrointestinal Tract		Acute gastrointestinal hemorrhage may present as hematemesis, hematochezia or malena.
Serious	Joints	70-80%	Joint bleed (Hemoarthrosis) may contribute to sustained hemophilic arthropathy, leading to pain and decreased mobility.
	Muscles	10-20%	May occur in deep compartments, such as iliopsoas, calf and forearm, and cause muscle and nerve damage.

IX, this results in a reduction of thrombin production and reduced blood clot formation. Under normal circumstances of an injury to blood vessels, natural clotting factor helps to form a strong platelet plug with stable fibrin clot formation over the platelet plug to stop bleeding. In patients with hemophilia, the lack of natural clotting factor causes incomplete or delayed fibrin clot formation, leading to prolonged bleeding.[2,12]

CLINICAL MANIFESTATIONS

There are several signs and symptoms of hemophilia, including bruising, hematoma, repeated bleeding into muscles and joints, spontaneous internal bleeding and excessive bleeding following injury or surgery.[13,14]

The severity of bleeding in hemophilia is generally correlated with the baseline clotting factor level, characterized into mild, moderate and severe as listed in **Table 1**.[1,3] 50-60% of patients present with severe form of hemophilia and may experience spontaneous bleeding into joints or muscles.[1] In moderate hemophilia, patients may have occasional spontaneous bleeding or prolonged bleeding with minor trauma. While for patients with mild hemophilia, they may not have excessive bleeding until major trauma or surgery.[3,12] Therefore, it is essential to maintain a high level of clotting factor to reduce the risk of spontaneous bleeding.[15]

The sites of bleeding in hemophilia and corresponding frequency are shown in **Table 2**.[1,14] The major sites of bleeding are internally into the joints or muscles. Bleeding may also occur in central nervous system, eye, mucous membranes, neck, throat, gastrointestinal tract, and renal system. Bleeding occurring in the central nervous system, neck, throat and gastrointestinal tract is considered to be life-threatening and require immediate treatment.[14,16-18]

MANAGEMENT APPROACH OF HEMOPHILIA

Comprehensive care helps in achieving optimal management of patients with hemophilia. Comprehensive care is comprised of both pharmacological and non-pharmacological management. It promotes physical and psychosocial health and decreases morbidity.[19-21] Comprehensive care by multi-disciplinary team of healthcare professionals should be instituted as soon as the diagnosis of hemophilia is made. Patients should have an annual checkup for a complete hematologic, musculoskeletal and psychosocial assessment so as to develop individual's management plan.[1]

The optimal management of hemophilia is complex. Despite episodic treatment to bleeding, continuous prophylaxis of hemophilia has also proven to provide clinical benefits.[22-24] Episodic treatment refers to on demand treatment to be given at the time of clinically evident bleeding. Continuous prophylaxis is the regular treatment to prevent anticipated bleeding. Prophylaxis may be further divided into primary prophylaxis, secondary prophylaxis, tertiary prophylaxis and intermittent prophylaxis. The detailed definitions of various type of management are listed in **Table 3**.[1] Several trials have proven that prophylactic therapy is effective in lowering bleeding risk, reducing long-term complications and hospitalization.[25-31] There are a number of consideration factors in the choice of replacement therapy, which should be based on the inhibitor status, severity of disease and individual response of patients.[32]

Table 3. Management approach of hemophilia[1]	
Types	**Definition**
Episodic (on demand) treatment	Therapy given at the time of bleeding.
Continuous (regular) prophylaxis	Therapy given to prevent bleeding for at least 45 of 52 weeks (85%) of a year.
• Primary prophylaxis	Continuous prophylaxis started before age of threeand before the second large joint bleed.
• Secondary prophylaxis	Continuous prophylaxis started after two or more large joint bleeds but before the onset of chronic arthropathy.
• prophylaxis	Continuous prophylaxis started after onset of arthropathy to prevent further damage.
Intermittent (periodic) prophylaxis	Therapy given to prevent bleeding for short periods of time such as during and after surgery.

PHARMACOLOGICAL MANAGEMENT OF HEMOPHILIA

Clotting Factor Concentrates

Factor VIII and factor IX concentrates are the treatment of choice for hemophilia A and B respectively since the 1990s.[1] As patients with hemophilia have deficiency in clotting factors, replacement with recombinant human factor or plasma-derived factor concentrates would be the treatment option. The use of recombinant factor or viral-inactivated plasma-derived factor concentrates is preferred over cryoprecipitate or fresh frozen plasma.[1] There is no preference for recombinant factor over plasma-derived products and the choice among various factor replacement products is based on safety, purity, product half-life, individual product characteristics, risk of inhibitor development, patient response and cost.[33,34]

Desmopressin (DDAVP)

Desmopressin is a synthetic analog of vasopressin which promotes the release of factor VIII and its carrier protein von Willebrand factor. Desmopressin is effective for patients with mild or moderate hemophilia A.[3,35-38] It does not affect Factor IX and should not be used in hemophilia B patients. In patients with severe, life-threatening bleeding, clotting factor concentrates is preferred over desmopressin, as the response to desmopressin is not immediate and the incremental increase in Factor VIII is insufficient for hemostasis. Individual response to desmopressin should be tested prior to therapeutic dose due to large inter-individual variability.[39,40] The benefits of desmopressin over clotting factor concentrates are lower cost and absence of risk of transmission of viral infections.[1] As desmopressin has antidiuretic activity and can cause hyponatremia, water intake is restricted and serum sodium levels should be monitored.[41]

Anti-fibrinolytics

Anti-fibrinolytic drugs like tranexamic acid and epsilon aminocaproic acid can be used as an adjunct therapy to control bleeding episodes. The drugs competitively inhibit the activation of plasminogen to plasmin and promote clot stability. The use of anti-fibrinolytics is particularly useful for bleeding episodes that involve mucosal membranes such as mouth, nose and bladder.[42-45] In comparison with tranexamic acid, epsilon aminocaproic acid has a shorter half-life, less potent and with more adverse reactions such as gastrointestinal upset and myopathy.[42]

CHALLENGES OF HEMOPHILIA MANAGEMENT – INHIBITORS

Patients with hemophilia may develop neutralizing inhibitors directed against factor VIII or factor IX. 25-30% of patients with hemophilia A develop anti-factor VIII inhibitors while factor IX inhibitors have been reported in approximately 3-5% of patients with hemophilia B.[24,46-48] The presence of inhibitor is confirmed by Bethesda inhibitor assay and classified into low-responding or high-responding. Low responders have persistently less than five Bethesda units of inhibitor level that do not increase even after stimulation of the immune system. High responders develop titers above five Bethesda units. For low responders, patients may continue to respond to clotting factor concentrates. On the other hand, the presence of high level of inhibitors in high responders renders clotting factor concentrates ineffective.[48-50] Alternatives should be considered in these patients, such as bypassing agents, immune tolerance induction or other agents.

Bypassing agents

Bypassing agents are generally the treatment of choice in hemophilia patients with high-titer inhibitor.[1] Bypassing products are the pro-thrombotic clotting factors that augment other parts of the coagulation cascade, bypassing the specific requirement for factor VIII or factor IX. Examples of bypassing agents include activated prothrombin complex concentrates and recombinant factor VIIa. In FENOC trial, the efficacy of both activated prothrombin complex concentrates and recombinant factor VIIa has been shown to be essentially equivalent in joint bleeding.[51]

Activated prothrombin complex concentrates are plasma-derived clotting factors containing factor II, IX, X and activated Factor VII. Activated prothrombin complex concentrates have been reported to be effective for 60-90% of musculoskeletal bleeds as well as surgery

prophylaxis.[52] However, in doses of greater than 200 units per kilogram per day or in patients with thrombotic risk factors, thromboembolic events like venous thrombosis, pulmonary embolism, myocardial infarction and stroke may occur. Its use is contraindicated in patients with disseminated intravascular coagulation and acute thrombosis or embolism.[53]

Recombinant factor VIIa has shown to be effective in the treatment of joint hemorrhage, life-threatening bleeding and surgical bleeding.[52] As it has short-acting pharmacokinetic properties, frequent administration of every 2-6 hours may be required to control bleeding episodes.

Immune Tolerance Induction

Immune tolerance is a process to accomplish inhibitor eradication as a long-term management. Immune tolerance induction is comprised of repetitive and frequent doses of factor VIII or IX over a long period of time, in an effort to tolerize the immune system and reduce inhibitor production. Immune tolerance induction is effective in 70-85% for factor VIII inhibitors but with only 30% for factor IX inhibitor.[54,55] Although immune tolerance induction regimens appear to be less successful in Asians, it should still be considered and used in appropriate patient population.[56] Potential influencing factors for the success of immune tolerance induction are age, duration after inhibitor detection and titer at start of therapy.[57]

Emicizumab

Emicizumab is a novel agent approved by Food and Drug Administration in November 2017 for the prophylaxis in hemophilia A patients with inhibitors. It is a recombinant humanized bispecific monoclonal antibody, replaces the action of factor VIIIa to bind with factor IXa and factor X to allow factor X activation and downstream hemostasis.[58] Factor VIII inhibitors do not bind to or neutralize emicizumab and have no impact on its hemostatic activity. As emicizumab restores the function of factor VIII as its mechanism of action, it is approved only for hemophilia A but not hemophilia B patients.

Due to its pharmacokinetic properties, emicizumab can be administered subcutaneously in a once-weekly interval, which is less frequent than other currently available hemophilia A therapies. It is used for prophylaxis and not effective for use in acute bleeding as loading dose is needed to achieve steady state. In HAVEN 1 trial, emicizumab prophylaxis was associated with a significantly lower bleeding rate than no prophylaxis in patients with hemophilia A with inhibitors. Emicizumab has also shown significant improvement in bleeding rate over bypassing agent prophylaxis in intra-individual comparison.[59] Concerning the safety of emicizumab, cases of thrombotic microangiopathy and thrombotic events were reported when a cumulative amount of more than 100 units per kilogram per day of activated prothrombin complex concentrate was administered to patients receiving emicizumab prophylaxis. It is recommended to avoid the concurrent use of emicizumab and activated prothrombin complex concentrate if the dose of activated prothrombin complex concentrate exceeds 100 units per kilogram per day. Recombinant factor VIIa would be preferred for the treatment of bleeding episodes in these patients.[59] Several clinical trials are on-going to further access the efficacy and safety of emicizumab in various populations. As clinical experience with emicizumab is limited to date and the safety profile is being characterized, patients should be monitored closely with adverse drug reactions.[58]

MEDICATIONS TO BE AVOIDED

Medications that increase the risk of bleeding should generally be avoided in patients with hemophilia, including anticoagulants, aspirin, non-steroidal anti-inflammatory drugs and herbal supplements such as ginkgo biloba, ginseng, and feverfew.[1] The above medications should only be used after consultation with hematologist for whom benefits are thought to outweigh the risks. Pain can be managed with alternatives like paracetamol and codeine. For patients with pain due to chronic hemophilia arthropathy, the use of cyclooxygenase-2 inhibitors may provide benefit while other non-steroidal anti-inflammatory drugs should be avoided.[60,61]

NON-PHARMACOLOGICAL CARE

Apart from pharmacological management, non-pharmacological care also places a role in patients with hemophilia. Special precautions should be taken for physical activities and dental care. Besides, adjunctive management such as first aid measures and physiotherapy are particularly important for management of bleeding in muscles and joints.[1]

Physical activity is encouraged in hemophilia patients to promote physical fitness and neuromuscular development. Appropriate exercise regimen should be designed as daily routine. Benefits of physical activities include muscle strengthening, improved coordination, maintenance of healthy weight, cardiovascular risk reduction and positive effects on bone density. Patients with significant musculoskeletal dysfunction are encouraged to perform weight-bearing exercise

in order to promote bone density. High contact sports such as rugby, boxing and soccer are best avoided. Target jointed can be protected with braces or splints to minimize the potential for life-threatening injuries.[62-64]

Appropriate dental care is essential in patients with hemophilia to prevent periodontal disease and dental caries. Patients should be educated with proper techniques for oral hygiene and conduct routine dental check to reduce the risk of gum bleeding. Dental extraction or surgical procedures within oral cavity should be performed in consultation with hematologist.[65-67]

THERAPIES UNDER DEVELOPMENT

There are several therapies under various stages of conceptualization or development for the management of bleeding in hemophilia patients, including gene therapy, cellular therapy and concizumab.

Gene therapy is designed to introduce exogenous genetic material into cells to compensate for abnormal gene and produce missing protein. Hemophilia is highly amenable to gene therapy as a modest increase in factor levels can lead to major effects on bleeding risks. Three studies have demonstrated significant reduction in bleeding rate and increase in factor levels by gene therapy.[68-70]

Cellular therapy is the transplantation of human cells to replace or repair damaged cells. In an animal model of hemophilia A, transplantation of liver endothelial cells has demonstrated increase in factor level and correction of bleeding phenotype.[71]

Concizumab is a monoclonal antibody targeted against tissue factor pathway inhibitor, which can lead to increase in procoagulant activity. Clinical efficacy in hemostasis has been demonstrated in preclinical studies and in vitro studies.[72,73] In an initial clinical trial, concizumab was well-tolerated without serious adverse events.[72]

CONCLUSION

Hemophilia is a bleeding disorder caused by the deficiency of clotting factors. The optimal management of patients with hemophilia is complex and the choice of therapy should be individualized based on inhibitor status, severity of disease and patient's response. The management approach of hemophilia is comprised of episodic treatment and continuous prophylaxis. Clotting factor concentrates are the treatment of choice for patients with hemophilia. Desmopressin is indicated for patients with mild to moderate hemophilia A while anti-fibrinolytic drugs are used as adjunct therapy. Development of neutralizing inhibitors is a big challenge in hemophilia management. Bypassing agents such as activated prothrombin complex concentrates and recombinant factor VIIa or immune tolerance induction would be the treatment options in patients with high-titer inhibitor. The management approach of hemophilia is keeping updated with technology. Emicizumab is the most currently approved agent for hemophilia with many other therapies under developmental stage for hemophilia management.

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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

Management Approach of Hemophilia A and B

1. ***Which of the following clotting factor deficiency results in hemophilia A?***
   A. Deficiency of clotting factor VII
   B. Deficiency of clotting factor VIII
   C. Deficiency of clotting factor IX
   D. Deficiency of clotting factor X

2. ***Which of the followings is the major bleeding site in hemophilia?***
   A. Gastrointestinal tract
   B. Central nervous system
   C. Joints
   D. Neck / throat

3. ***Which of the following statements regarding the management approach of hemophilia is / are CORRECT?***
   (i) The choice of therapy should be individualized, based on the inhibitor status, severity of disease and patient's response.
   (ii) Continuous prophylaxis is given for at least 45 out of 52 weeks in a year.
   (iii) Secondary prophylaxis is started after the onset of arthropathy.

   A. (ii) only
   B. (i) and (ii)
   C. (i) and (iii)
   D. (ii) and (iii)

4. ***Which of the followings is the treatment option for patients with hemophilia B?***
   A. Factor IX concentrates
   B. Desmopressin
   C. Emicizumab
   D. Dabigatran

5. ***Which of the followings is / are the treatment option(s) for hemophilia patients with high-titer inhibitors?***
   A. Immune tolerance induction
   B. Recombinant factor VIIa
   C. Activated prothrombin complex concentrates
   D. All of the above

6. ***Which of the following statements regarding desmopressin is / are CORRECT?***
   (i) Desmopressin is a synthetic analog of antidiuretic hormone vasopressin.
   (ii) Desmopressin is used in patients with mild or moderate hemophilia A and B.
   (iii) A test dose of desmopressin can be given prior to therapeutic dose to determine individual response.

   A. (i) only
   B. (ii) only
   C. (i) and (iii)
   D. (ii) and (iii)

7. ***Which of the following statements regarding bypassing agent is INCORRECT?***
   A. Bypassing agents can be used in hemophilia patients with high-titer inhibitor.
   B. Activated prothrombin complex concentrates contain factor II, IX, X and activated factor VIII.
   C. Activated prothrombin complex concentrates may be associated with thromboembolic events when used in doses greater than 200 units per kilogram per day.
   D. Recombinant factor VIIa has shorter half-life than activated prothrombin complex concentrates.

8. ***Which of the following statements regarding emicizumab is CORRECT?***
   A. The route of administration of emicizumab is intravenous.
   B. Emicizumab is effective for use in acute bleeding episodes.
   C. Emicizumab is approved by FDA for prophylaxis in hemophilia A patients without inhibitors.
   D. Emicizumab is a bispecific monoclonal antibody that bridges factor IXa and factor X.

9. ***Which of the following medication(s) should be avoided in patients with hemophilia?***
   (i) Anticoagulants
   (ii) Non-steroidal anti-inflammatory drugs (NSAIDs)
   (iii) Tranexamic acid

   A. (iii) only
   B. (i) and (ii)
   C. (i) and (iii)
   D. (ii) and (iii)

10. ***Which of the following therapies is/ are under developmental stage for patients with hemophilia?***
    A. Gene therapy
    B. Cellular therapy
    C. Concizumab
    D. All of the above

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 252(D&T)

Review of Newly Registered Anticoagulants and a Reversal Agent for Dabigatran: Bivalirudin, Edoxaban and Idarucizumab

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

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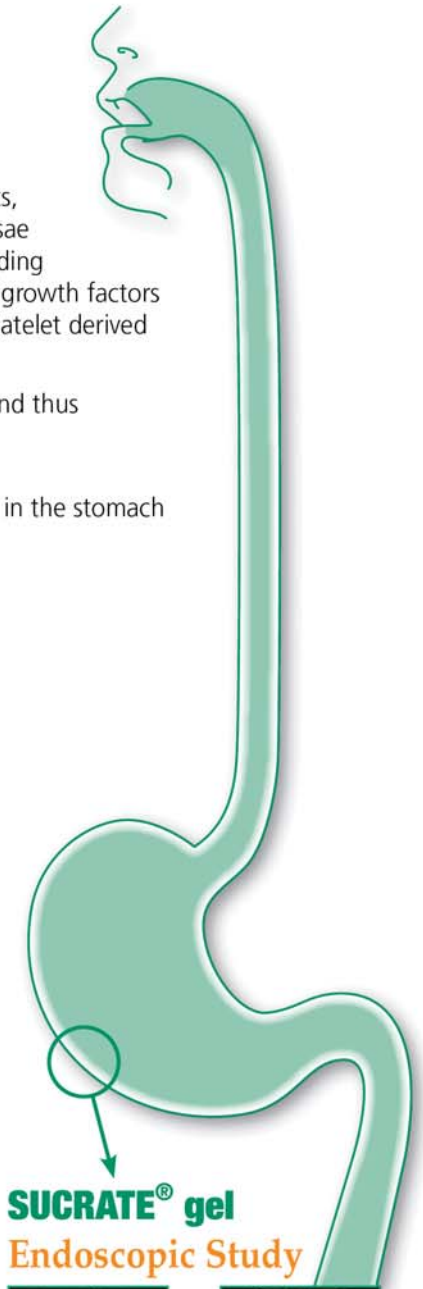

Cosentino F. et al., Società Italiana di Endoscopia Digestiva, VII Simp. Naz, Napoli, 1992

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A comparative Study of HBV-DNA Quantification from Chronic HBV Infected Patients using COBAS TaqMan and GenoQuant HBV Real-Time PCR

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ABSTRACT

Quantification of hepatitis B virus (HBV) DNA in human serum or plasma is of high value for detecting HBV infection and monitoring antiviral treatment efficacy. Due to the high cost of HBV diagnosis and treatment, a reliable, precise and sensitive diagnostic test is crucial to patients. In this study, the new Diagcor GenoQuant™ HBV Real-Time PCR assay was compared to the Roche COBAS® TaqMan® HBV assay with 369 serum samples from patients with chronic hepatitis B infection in Bangladesh. Results indicated a high concordant rate of 96.91% within the dynamic range of the two real-time PCR assays. The GenoQuant™ HBV Real-Time PCR test showed comparable sensitivity and a broader dynamic range than the COBAS® TaqMan® HBV assay. By coupling high sensitivity with an extended dynamic range, the GenoQuant™ HBV Real-Time PCR assay provides an accurate, reliable and low-cost nucleic acid amplification testing for HBV infected patients.

Keywords: *Hepatitis B Virus, DNA Quantification, Chronic Hepatitis, Molecular Diagnostics, Real-Time PCR, Antiviral Treatment Monitor*

INTRODUCTION

Hepatitis B virus (HBV) is a small partially double-stranded virus belongs to the family of the *Hepadnaviridae* that can induces acute or chronic hepatitis.[1] It has been reported that over 2 billion people throughout the world are HBV infected, and over 350 million of them are chronically infected carriers.[2] Chronic carriers are at increased risk of progression to chronic hepatitis, cirrhosis and hepatocellular carcinoma.[3-5] The determination of HBV-DNA levels in human serum or plasma has become the most straightforward and reliable method used for accurate diagnosis and prognosis of acute and chronic HBV infection.[6] Measurement of HBV levels in serum also plays a vital role in the management of patients receiving antiviral drugs, such as monitoring antiviral therapy response and identifying the occurrence of drug resistance in patients.[7, 8]

Unlike the antibody test, nucleic acid amplification testing (NAAT) is sensitive, specific and rapid, which allows early detection of HBV virus DNA before the production of HBV antibody by the human body. That is, NAAT reduces the duration of the pre-seroconversion window period.[9, 10] Real-time PCR is a new molecular tool that offers highly sensitive quantitative analysis. It is progressively replacing endpoint PCR systems for monitoring patients with chronic hepatitis B since it allows absolute quantification of the HBV viral load with a broad dynamic range, high sensitive, definite and rapid result.[11, 12] Quantification by real-time PCR is based on the determination of the threshold cycle (C_t) at which amplification is first detected at the early exponential phase.[13] In this case, the quantification of the viral load is much more decisive than that measured with endpoint PCR systems.[14, 15]

In therapeutic practice, patients suffering from HBV infection need to perform HBV DNA quantitative test to monitor the viral load repeatedly. Sometimes alternative

tests are required until the complete clearance of the hepatitis B virus represented by a negative result of HBs antigen.[16] As far as we know, numerous researchers and laboratories/companies have reported several in-house and commercial HBV real-time PCR tests/ kits.[11-13, 17-22] However, the cost of current HBV-DNA tests is prohibitive, which places a heavy medical burden on the patients and the public. Thus, a valid test with lower cost for HBV infected patients would be of great benefit. Our study aimed to evaluate the performance of DiagCor GenoQuant™ HBV Real-Time PCR assay for the detection and quantification of HBV-DNA in serum samples and to compare these results with COBAS® TaqMan® HBV test from Roche Molecular Diagnostics.

MATERIALS AND METHODS

Three hundred and sixty-nine blood samples were obtained from patients with chronic HBV infection who visited the Molecular Diagnostic Laboratory of Popular Diagnostic Centre, Dhaka, Bangladesh. Blood samples were collected in a BD Vacutainer tube. After centrifugation, the serum was divided into two aliquots of 1 ml each and then extracted for DNA. A known DNA copy number of HBV quantitation standard (QS) were introduced in each specimen during the extraction.[11] Roche High Pure Viral Nucleic Acid (manual) extraction kit was used to extract HBV-DNA from 500 µL of blood serum. The obtained DNA samples were further examined by DiagCor and COBAS® TaqMan® HBV Real-time PCR assays, respectively. **Figure 1** shows the flowchart of clinical samples detection method. Both systems utilize a hybridization probe with a fluorescent moiety covalently linked to the 5′ end of the probe (reporter) and a quenching moiety bound to the 3′ end of the probe (quencher). Probe hybridization and primer extension coincide in the presence of target. The fluorescent signal is generated by removing the reporter through the 5′→3′ exonuclease activity of a thermostable *Taq* DNA polymerase.[5, 11] Quantitation of HBV-DNA is performed using the HBV QS. The system quantifies the amplicons during the exponential phase of amplification by recording the fluorescence signal with a fluorescence detector in real time condition. During the PCR cycle, an increase in normalized fluorescence of a sample exceeds the background noise is considered as the critical C_t, which indicates the beginning of the exponential growth phase of the detection signal.

COBAS® TaqMan® HBV Test

Extracted DNA samples were subjected to the COBAS® TaqMan® HBV real-time PCR assay according to the user manual (Roche, USA). In this assay, HBV DNA and the HBV QS were amplified simultaneously. Results were displayed as an international unit per milliliter (IU/mL). The limit of detection of the assay was set as 6 IU/mL with the dynamic range from 29 to 1.10E+08 IU/mL. The test fulfills the current requirements of a highly sensitive HBV DNA detection method according to the International WHO Standard to provide reliable quantification of HBV genotypes A–G with extensive measuring range. Laborious repeat testing is minimized as well.

GenoQuant™ HBV Real-Time PCR Kit

Extracted DNA samples were tested using GenoQuant™ HBV Real-Time PCR (DiagCor, Hong Kong) following the manufacturer's instructions. A total of 369 specimens were blind tested by DiagCor using ABI ViiA7 real-time

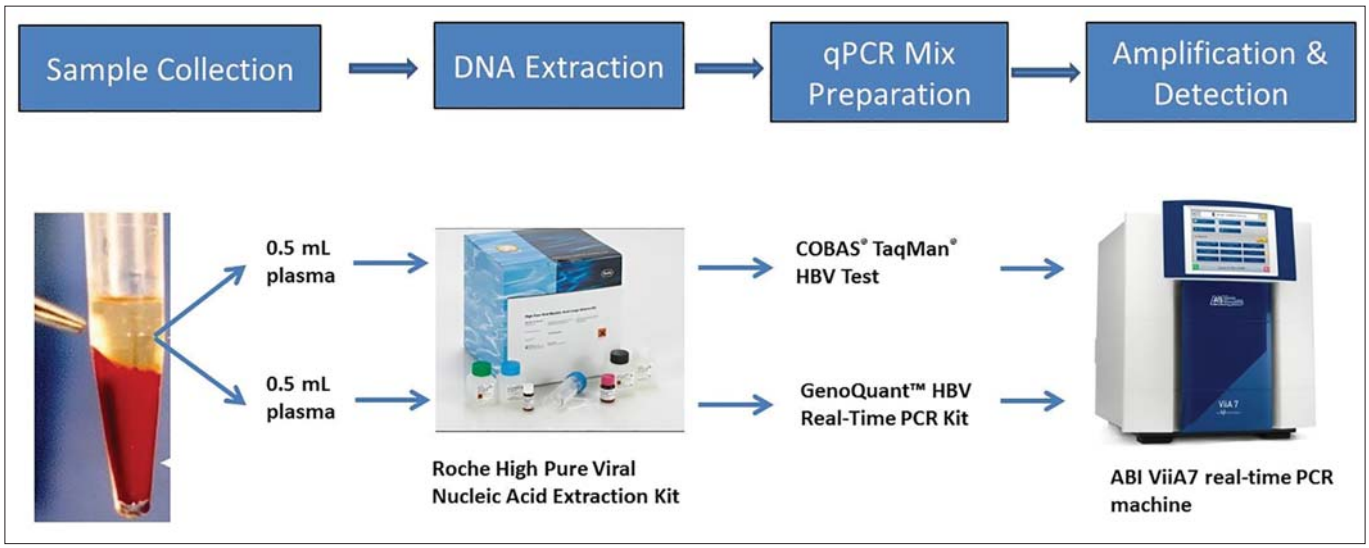

Figure 1. Flowchart of clinical samples detection method.

PCR machine (Applied Biosystems, Foster City, CA, USA). Two targets of HBV DNA and internal amplification control were amplified simultaneously in each sample. A four-point external standard set was used to calculate the initial copy number of the samples. The result was reported in IU/mL. The limit of detection was set at 10 IU/mL with a dynamic range from 10 to 1.0E+08 IU/mL.

RESULTS AND DISCUSSION

A total of 369 samples from a Bangladesh laboratory were determined by using our DiagCor GenoQuant™ HBV Real-Time PCR kit for the presence and quantity of HBV DNA. The results were further compared with COBAS® TaqMan® HBV Test. Of the 369 samples, 94 samples were negative or with viral load values below the limit of detection (LOD, <6 IU/mL). A total of 338 samples were detected by GenoQuant™ HBV Real Time assay, with a relative sensitivity of 95.21%.

Table 1 shows the detailed comparisons between Diagcor GenoQuant™ test and Roche Cobas® TaqMan® assay. For the latter assay, 233 of the 369 samples (63.14%) were detected with HBV DNA within the dynamic range of 29 to 1.10E+08 IU/mL. About 118 samples were below the lower limit of the linear range of the test, in which 94 samples were below the LOD of the assay (<6 IU/mL) and 24 samples were detected within the low HBV viral load range of 6-29 IU/mL. Eighteen samples were above the upper limit of quantification (>1.10E+08 IU/mL). HBV DNA was detected and quantifiable in 286 samples (77.51%) using Diagcor GenoQuant™ Real-Time assay, showing a slightly broader linear quantification range than that of Cobas® TaqMan® assay. Results indicated that 46 (30+16) out of 286 samples had viral loads below the lower limit of the dynamic range (<29 IU/mL) while 7 out of 286 samples showed viral loads above the upper limit of the dynamic range (>1.10E+08 IU/mL) of the Cobas® TaqMan® assay. For those 30 samples with viral loads below LOD and 7 samples above the upper dynamic range by Cobas® TaqMan® assay, their HBV viral loads were found to be ranged from 10.3 to 420 IU/mL, and from 2.43E+06 to 9.72E+07 IU/mL using Diagcor GenoQuant™ Real-Time assay, respectively. Using Diagcor GenoQuant™ Real-Time assay, 72 samples were below the LOD of the test (<10 IU/mL), and 11 samples were above the upper limit of quantification (>1.10E+08 IU/mL).

An excellent correlation (R^2 = 0.9691) was obtained when the linear regression analysis was carried out according to the 233 paired quantitative results available for both tests **(Figure 2)**. The regression line showed the following equation: GenoQuant™ HBV Real-Time (log IU/mL) = 0.972 x COBAS® TaqMan® HBV (log IU/mL) + 0.3289. The mean difference of assay result (GenoQuant™ – COBAS®) was -0.24 log IU/mL ranging from -1.46 to +1.00, with a standard deviation of 0.27 log IU/mL. Comparing the results from both assays, it showed that 91 and 99% of the samples were different by less than 0.5 and 1 log, respectively. Detailed results of each sample are listed in the supplementary data **Table 1S**.

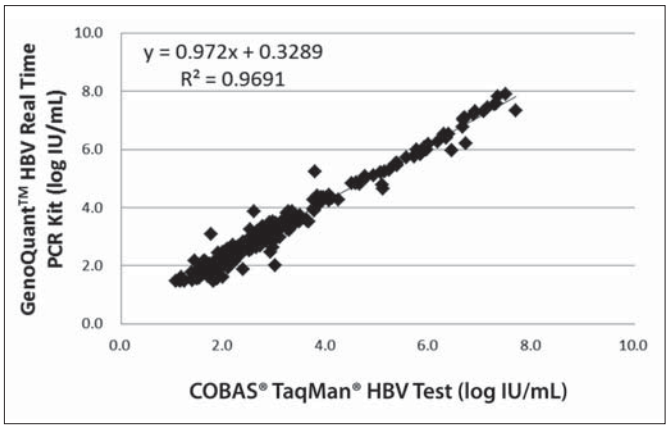

Figure 2. Linear regression analysis performed on 233 samples with quantitative results obtained by the two assays.

Table 1. Comparison between GenoQuant™ HBV Real-Time PCR Kit and COBAS® TaqMan® HBV Test

		COBAS® TaqMan® HBV Test				
		< 6 IU/mL	6-29 IU/mL	Within dynamic range (29- 1.10E+08 IU/mL)	>1.10E+08 IU/mL	Total
GenoQuant™ HBV Real-Time PCR	<10 IU/mL	64	8[a]			72
	Within dynamic range (10-1.0E+08)	30[b]	16[c]	233	7[d]	286
	>1.0E+08 IU/mL				11	11
	Total	94	24	233	18	369

[a] COBAS® TaqMan® results ranged from 6 to 15.9 IU/mL.
[b] GenoQuant™ HBV results ranged from 10.3 to 420 IU/mL.
[c] COBAS® TaqMan® results ranged from 6.13 to 25.1 IU/mL; GenoQuant™ HBV results ranged from 10.1 to 87.6 IU/mL.
[d] GenoQuant™ HBV results ranged from 2.43E+06 to 9.72E+07 IU/mL.
Remark: Detailed results are listed in supplementary data (Table 1S).

Supplementary data

Table 1S. Results of GenoQuant™ HBV Real-Time PCR Kit and COBAS® TaqMan® HBV Test

Number	Sample ID	GenoQuant™ Result (IU/mL)	COBAS® TaqMan® Result (IU/mL)	Number	Sample ID	GenoQuant™ Result (IU/mL)	COBAS® TaqMan® Result (IU/mL)
1	8850	1.44E+03	3.96E+03	39	9448	1.08E+02	3.23E+02
2	9409	4.33E+01	1.44E+02	40	9449	2.70E+01	1.47E+02
3	9410	7.23E+02	2.15E+03	41	9450	8.42E+00	<6.00E+00
4	9411	1.26E+03	1.94E+03	42	9451	3.58E+02	1.07E+03
5	9412	4.98E+06	1.26E+07	43	9452	1.50E+02	5.01E+02
6	9413	2.24E+05	3.23E+05	44	9453	4.52E+03	3.37E+03
7	9414	4.47E+00	<6.00E+00	45	9454	2.80E+08	>1.10E+08
8	9415	7.40E+01	3.58E+01	46	9455	1.22E+03	9.52E+02
9	9416	1.84E+02	4.39E+02	47	9456	4.14E+01	6.50E+01
10	9417	8.86E+02	4.13E+02	48	9457	8.63E+00	<6.00E+00
11	9418	2.19E+03	7.37E+03	49	9458	6.70E+03	2.54E+04
12	9419	5.60E+05	9.74E+05	50	9459	4.71E+00	<6.00E+00
13	9420	4.18E+02	8.07E+02	51	9460	2.45E+00	<6.00E+00
14	9421	2.36E+02	7.54E+01	52	9461	1.35E+01	3.15E+01
15	9422	2.33E+02	6.54E+02	53	9462	1.68E+03	1.85E+03
16	9423	0.00E+00	N.D.	54	9463	1.27E+02	3.63E+02
17	9424	2.06E+02	4.68E+02	55	9464	0.00E+00	N.D.
18	9425	8.01E+00	7.84E+00	56	9465	9.09E+02	3.22E+03
19	9426	2.16E+00	<6.00E+00	57	9466	0.00E+00	<6.00E+00
20	9427	9.31E+01	2.64E+02	58	9467	2.39E+01	3.14E+01
21	9428	4.22E+00	<6.00E+00	59	9468	7.88E+02	3.00E+03
22	9429	1.71E+01	2.90E+01	60	9469	1.79E+03	7.24E+03
23	9430	8.10E+05	1.19E+06	61	9470	0.00E+00	N.D.
24	9431	7.66E+00	N.D.	62	9471	2.43E+06	>1.10E+08
25	9432	0.00E+00	<6.00E+00	63	9472	2.36E+06	3.43E+06
26	9433	0.00E+00	N.D.	64	9473	2.89E+02	<6.00E+00
27	9434	1.29E+04	2.07E+04	65	9474	1.83E+08	>1.10E+08
28	9435	5.72E+00	<6.00E+00	66	9475	1.49E+01	<6.00E+00
29	9436	3.67E+04	6.82E+04	67	9476	4.30E+02	7.79E+02
30	9437	4.12E+00	N.D.	68	9477	8.53E+02	6.10E+02
31	9438	1.92E+03	6.40E+03	69	9478	4.58E+01	1.29E+02
32	9439	0.00E+00	N.D.	70	9479	9.00E+02	1.26E+03
33	9440	4.40E+02	1.56E+03	71	9480	5.51E+04	9.10E+04
34	9442	2.98E+01	5.37E+01	72	9481	6.14E+01	1.15E+02
35	9443	1.05E+01	<6.00E+00	73	9482	4.60E+08	>1.10E+08
36	9444	6.43E+03	1.61E+04	74	9483	6.33E+03	2.08E+04
37	9445	9.71E+01	2.64E+02	75	9484	4.09E+02	6.33E+02
38	9447	6.09E+02	7.60E+02	76	9485	1.36E+07	2.75E+07

Number	Sample ID	GenoQuant™ Result (IU/mL)	COBAS® TaqMan® Result (IU/mL)	Number	Sample ID	GenoQuant™ Result (IU/mL)	COBAS® TaqMan® Result (IU/mL)
77	9486	2.64E+02	4.78E+02	118	10269	2.79E+02	5.07E+02
78	9487	5.60E+04	1.16E+05	119	10270	2.04E+02	4.82E+02
79	9488	1.46E+01	3.97E+01	120	10271	8.52E+01	1.20E+02
80	9489	1.55E+01	2.38E+01	121	10272	8.70E+00	<6.00E+00
81	9490	1.01E+04	2.26E+04	122	10273	6.24E+00	1.25E+01
82	9491	1.50E+02	2.94E+02	123	10274	0.00E+00	N.D.
83	9492	1.33E+01	<6.00E+00	124	10275	2.21E+00	<6.00E+00
84	9493	1.99E+08	>1.10E+08	125	10276	2.09E+03	3.13E+03
85	9494	7.48E+00	6.00E+00	126	10277	4.22E+03	3.42E+03
86	9495	2.58E+01	4.15E+01	127	10278	1.30E+01	1.01E+01
87	9496	7.22E+06	1.61E+07	128	10279	0.00E+00	N.D.
88	9497	0.00E+00	N.D.	129	10280	1.93E+03	3.36E+03
89	9498	1.75E+03	4.65E+03	130	10281	2.93E+03	3.26E+03
90	9499	4.23E+02	4.34E+02	131	10282	1.89E+07	3.41E+07
91	9500	2.39E+05	3.29E+05	132	10283	4.60E+00	<6.00E+00
92	9501	0.00E+00	N.D.	133	10284	1.51E+01	<6.00E+00
93	9502	9.20E+00	<6.00E+00	134	10285	3.36E+01	<6.00E+00
94	9503	5.52E+00	<6.00E+00	135	10286	2.04E+08	>1.10E+08
95	9504	5.11E+01	8.41E+01	136	10287	3.87E+00	1.06E+01
96	9505	1.85E+00	<6.00E+00	137	10288	3.38E+01	<6.00E+00
97	9506	5.79E+02	1.40E+03	138	10289	2.37E+05	2.77E+05
98	9507	0.00E+00	<6.00E+00	139	10290	5.61E+03	8.96E+03
99	9508	5.46E+00	<6.00E+00	140	10291	1.33E+05	1.77E+05
100	9509	8.03E+01	1.25E+02	141	10292	1.52E+01	6.13E+00
101	9510	3.62E+01	7.23E+01	142	10293	5.61E+05	6.99E+05
102	9511	5.19E+02	8.29E+02	143	10294	1.98E+01	2.51E+01
103	9512	8.17E+02	2.99E+02	144	10295	1.91E+02	2.27E+02
104	9513	1.29E+01	<6.00E+00	145	10296	3.18E+02	6.51E+02
105	9514	5.93E+03	9.77E+03	146	10297	3.96E+01	5.31E+01
106	9515	1.68E+03	2.66E+03	147	10298	1.79E+02	2.73E+02
107	10258	1.01E+01	1.36E+01	148	10299	7.38E+02	1.16E+03
108	10259	9.90E+01	1.33E+02	149	10300	4.97E+01	<6.00E+00
109	10260	5.76E+02	2.23E+03	150	10301	6.84E+05	6.67E+05
110	10261	4.81E+01	1.21E+01	151	10302	1.51E+03	2.64E+03
111	10262	1.16E+02	<6.00E+00	152	10303	2.07E+02	3.99E+02
112	10263	4.68E+06	1.18E+07	153	10304	1.29E+02	2.93E+02
113	10264	2.39E+08	>1.10E+08	154	10305	0.00E+00	N.D.
114	10265	1.23E+05	6.04E+04	155	10306	7.32E+02	1.26E+03
115	10266	2.51E+03	5.21E+03	156	10307	5.24E+01	1.16E+02
116	10267	0.00E+00	<6.00E+00	157	10308	1.33E+01	<6.00E+00
117	10268	1.20E+03	2.20E+03	158	10309	1.43E+02	3.77E+02

Number	Sample ID	GenoQuant™ Result (IU/mL)	COBAS® TaqMan® Result (IU/mL)	Number	Sample ID	GenoQuant™ Result (IU/mL)	COBAS® TaqMan® Result (IU/mL)
159	10310	4.41E+01	<6.00E+00	200	10351	1.03E+03	2.91E+03
160	10311	0.00E+00	<6.00E+00	201	10352	2.11E+00	<6.00E+00
161	10312	2.98E+01	3.55E+01	202	10353	0.00E+00	<6.00E+00
162	10313	2.15E+00	N.D.	203	10354	4.10E+00	<6.00E+00
163	10314	1.24E+02	8.34E+01	204	10355	0.00E+00	<6.00E+00
164	10315	6.00E+03	1.73E+05	205	10356	1.54E+02	2.42E+02
165	10316	2.51E+00	<6.00E+00	206	10357	7.68E+01	2.80E+02
166	10317	3.81E+02	7.40E+03	207	10358	3.44E+01	<6.00E+00
167	10318	8.22E+01	1.11E+02	208	10359	8.70E+03	2.21E+04
168	10319	4.14E+09	>1.10E+08	209	10360	2.11E+07	>1.10E+08
169	10320	5.21E+06	1.63E+06	210	10361	8.70E+02	1.95E+03
170	10321	8.76E+01	6.44E+00	211	10362	4.55E+06	5.85E+06
171	10322	0.00E+00	<6.00E+00	212	10363	3.29E+02	1.75E+03
172	10323	2.06E+02	2.26E+02	213	10364	2.00E+07	3.62E+07
173	10324	1.15E+07	2.02E+07	214	10365	9.42E+00	7.58E+00
174	10325	8.94E+00	1.59E+01	215	10366	8.46E+02	9.59E+02
175	10326	6.18E+01	1.21E+02	216	10367	9.00E+05	9.76E+05
176	10327	8.16E+04	1.23E+05	217	10368	1.63E+02	1.37E+02
177	10328	9.42E+01	2.59E+02	218	10369	5.20E+01	1.08E+02
178	10329	1.75E+02	3.60E+02	219	10370	7.98E+03	2.14E+04
179	10330	1.33E+01	<6.00E+00	220	10371	2.00E+00	<6.00E+00
180	10331	1.13E+02	2.42E+02	221	10372	5.60E+03	1.88E+04
181	10332	4.94E+07	2.15E+07	222	10373	1.97E+01	1.40E+01
182	10333	1.24E+05	4.41E+04	223	10374	7.86E+03	2.25E+04
183	10334	2.96E+01	1.11E+01	224	10375	0.00E+00	<6.00E+00
184	10335	0.00E+00	<6.00E+00	225	10376	9.54E+05	1.54E+06
185	10336	1.13E+02	2.69E+02	226	10377	1.67E+03	6.58E+03
186	10337	0.00E+00	<6.00E+00	227	10378	2.52E+02	5.49E+02
187	10338	1.39E+00	<6.00E+00	228	10379	3.33E+01	3.87E+01
188	10339	3.66E+01	5.25E+01	229	10380	1.87E+00	<6.00E+00
189	10340	8.22E+01	7.44E+01	230	10381	2.49E+01	<6.00E+00
190	10341	9.72E+07	>1.10E+08	231	10382	3.57E+01	<6.00E+00
191	10342	6.00E+03	1.84E+04	232	10383	0.00E+00	<6.00E+00
192	10343	1.24E+08	>1.10E+08	233	10384	2.90E+02	5.23E+02
193	10344	3.86E+02	1.07E+03	234	10385	0.00E+00	<6.00E+00
194	10345	1.36E+03	2.36E+03	235	10386	1.73E+01	1.50E+01
195	10346	5.69E+01	4.08E+01	236	10387	1.95E+06	3.38E+06
196	10347	7.32E+07	>1.10E+08	237	10388	3.63E+01	8.19E+01
197	10348	0.00E+00	N.D.	238	10389	8.22E+00	1.25E+01
198	10349	0.00E+00	<6.00E+00	239	10390	9.84E+00	N.D.
199	10350	1.67E+03	2.92E+03	240	10391	4.65E+01	<6.00E+00

Number	Sample ID	GenoQuant™ Result (IU/mL)	COBAS® TaqMan® Result (IU/mL)	Number	Sample ID	GenoQuant™ Result (IU/mL)	COBAS® TaqMan® Result (IU/mL)
241	10392	2.16E+03	5.39E+03	282	10433	3.56E+07	>1.10E+08
242	10393	3.54E+02	3.75E+02	283	10434	0.00E+00	<6.00E+00
243	10394	3.06E+02	7.92E+02	284	10435	7.62E+08	>1.10E+08
244	10395	3.14E+02	3.36E+02	285	10436	4.72E+06	9.97E+06
245	10396	3.12E+02	8.90E+02	286	10437	1.72E+01	1.31E+01
246	10397	4.41E+02	6.46E+02	287	10438	4.95E+00	<6.00E+00
247	10398	5.90E+02	7.73E+02	288	10439	1.04E+02	2.02E+02
248	10399	1.16E+02	3.67E+02	289	10440	7.74E+03	1.47E+04
249	10400	3.58E+05	5.37E+05	290	10441	8.40E+02	1.71E+03
250	10401	3.50E+01	8.31E+01	291	10442	4.64E+02	7.45E+02
251	10402	0.00E+00	N.D.	292	10443	0.00E+00	N.D.
252	10403	1.62E+01	N.D.	293	10465	1.21E+02	2.22E+02
253	10404	7.92E+06	1.98E+07	294	10466	4.42E+01	8.53E+01
254	10405	6.24E+01	6.32E+01	295	10467	1.89E+03	1.70E+03
255	10406	1.14E+05	1.61E+05	296	10468	3.07E+07	8.06E+07
256	10407	2.00E+02	4.88E+02	297	10469	4.21E+03	3.78E+03
257	10408	2.28E+03	5.57E+03	298	10470	9.06E+02	1.20E+03
258	10409	4.13E+02	1.19E+03	299	10471	1.71E+01	<6.00E+00
259	10410	2.94E+03	3.41E+03	300	10472	4.35E+01	6.57E+00
260	10411	3.95E+00	N.D.	301	10473	1.00E+03	2.07E+03
261	10412	9.48E+01	2.96E+02	302	10474	6.06E+07	>1.10E+08
262	10413	4.46E+04	6.54E+04	303	10475	3.11E+04	6.74E+04
263	10414	1.32E+03	2.31E+03	304	10476	1.65E+02	3.62E+02
264	10415	1.12E+04	1.76E+04	305	10477	1.03E+01	<6.00E+00
265	10416	5.07E+04	8.20E+04	306	10478	4.13E+01	9.25E+01
266	10417	4.99E+02	1.66E+03	307	10479	8.16E+00	<6.00E+00
267	10418	1.49E+00	N.D.	308	10480	1.18E+03	1.92E+03
268	10419	1.96E+01	N.D.	309	10481	4.05E+00	<6.00E+00
269	10420	3.78E+02	9.08E+02	310	10482	1.00E+00	<6.00E+00
270	10421	9.66E+01	4.04E+01	311	10483	1.14E+04	2.68E+04
271	10422	1.93E+01	N.D.	312	10484	2.70E+06	9.38E+05
272	10423	2.94E+03	4.93E+03	313	10485	3.83E+04	7.38E+04
273	10424	4.15E+00	<6.00E+00	314	10486	2.48E+00	1.36E+01
274	10425	0.00E+00	<6.00E+00	315	10487	1.54E+01	<6.00E+00
275	10426	2.29E+00	<6.00E+00	316	10488	1.67E+01	<6.00E+00
276	10427	1.36E+03	2.18E+03	317	10489	6.24E+01	2.92E+01
277	10428	1.47E+06	1.81E+06	318	10490	7.02E+05	7.90E+05
278	10429	2.34E+01	5.70E+01	319	10491	1.15E+01	3.04E+01
279	10430	1.00E+02	1.87E+02	320	10492	3.35E+02	5.76E+02
280	10431	0.00E+00	N.D.	321	10493	1.99E+02	3.30E+02
281	10432	3.03E+03	5.53E+03	322	10494	4.87E+01	4.21E+01

Number	Sample ID	GenoQuant™ Result (IU/mL)	COBAS® TaqMan® Result (IU/mL)	Number	Sample ID	GenoQuant™ Result (IU/mL)	COBAS® TaqMan® Result (IU/mL)
323	10495	2.32E+03	3.40E+03	347	10519	6.18E+07	>1.10E+08
324	10496	8.10E+03	1.68E+04	348	10520	5.12E+05	5.70E+05
325	10497	1.01E+03	2.45E+03	349	10521	1.12E+01	<6.00E+00
326	10498	3.87E+01	4.87E+01	350	10522	6.78E+08	>1.10E+08
327	10499	2.44E+03	2.96E+03	351	10523	3.60E+02	6.84E+02
328	10500	9.06E+01	1.86E+02	352	10524	1.64E+01	2.06E+01
329	10501	1.70E+04	1.83E+04	353	10525	1.68E+03	3.53E+03
330	10502	1.36E+01	<6.00E+00	354	10526	4.20E+02	<6.00E+00
331	10503	3.93E+01	1.41E+02	355	10527	6.60E+01	1.44E+02
332	10504	6.24E+01	7.71E+01	356	10260 qsi	8.28E+02	2.23E+03
333	10505	9.66E+02	2.44E+03	357	10260 qsir	1.01E+03	2.23E+03
334	10506	4.74E+01	<6.00E+00	358	10484 R	2.78E+06	9.38E+05
335	10507	0.00E+00	<6.00E+00	359	8952 R	5.68E+01	1.23E+03
336	10508	1.42E+01	3.03E+01	360	9327 b	5.25E+02	1.01E+03
337	10509	2.19E+01	1.36E+01	361	9328 rb	2.18E+06	2.46E+06
338	10510	3.55E+01	6.19E+01	362	9373 rc	1.07E+01	1.38E+01
339	10511	1.37E+01	<6.00E+00	363	9374 rc	3.56E+08	>1.10E+08
340	10512	3.63E+01	8.95E+00	364	9375 rc	6.84E+03	1.67E+04
341	10513	1.88E+01	<6.00E+00	365	9376 rc	5.18E+02	4.95E+02
342	10514	5.76E+03	7.69E+03	366	9377 r	6.60E+01	1.36E+02
343	10515	1.73E+03	2.62E+03	367	9378 r	4.47E+02	7.86E+02
344	10516	1.67E+05	1.96E+05	368	9379 r	2.18E+07	6.42E+07
345	10517	1.41E+02	1.19E+02	369	9380 r	6.36E+01	2.90E+01
346	10518	1.00E+03	9.99E+01				

Remark: N.D. = Not detected.
COBAS® TaqMan® HBV-DNA conversion factor is: 1IU/mL = 5.82 copies/mL.
GenoQuant™ HBV-DNA conversion factor is: 1IU/mL = 3.99 copies/mL.

CONCLUSION

A total of 369 DNA samples were extracted from serum samples of chronic hepatitis B infection patients in Bangladesh and then amplified by two commercial HBV real-time PCR tests Roche COBAS® TaqMan® HBV Test and Diagcor GenoQuant™ HBV Real-Time assay, respectively. Results indicated that the newly developed GenoQuant™ HBV Real-Time PCR Kit showed similar performance but slightly broader dynamic range than that of COBAS® TaqMan® HBV Test. Moreover, results of Diagcor GenoQuant™ HBV Real-Time assay correlated exceptionally well (R^2 = 0.9691) with those of COBAS® TaqMan® HBV Test. By coupling an exquisite sensitivity with an extended linear quantification range of HBV DNA, we demonstrated the potential clinical usefulness of both assays in monitoring the antiviral therapy of patient with chronic hepatitis B.

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DECLARATION

The authors declare that the research methods and the results obtained in this study are pertinent and do not deliberately favor any brand mentioned in the manuscript.

Author's background

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SHPHK – Everyone can make a difference!

Reported by **Vienna Leung,** *Pharmacist of the Society of Hospital Pharmacists of Hong Kong*

Every year, the Society of Hospital Pharmacists of Hong Kong (SHPHK) would submit proposal to the Hong Kong Government for the Policy Address to voice concerns and needs of the pharmacy profession. In this year's proposal of SHPHK, there were huge emphases on the reinforcement of partnership between the public and private health sectors, and on the urgent needs to reduce the workload of doctors as well as to improve the safety and quality of patient care in HA hospitals by introduction of Pharmacist Clinics and Clinical Ward Pharmacists.

Over the past years, the pharmacy profession in Hong Kong has been facing a lot of challenges, for example, under-utilization of pharmacists' role in healthcare system, especially in primary care. It is important for us to work together in unity in order to turn challenges into opportunities! Therefore, the Society strongly encourages its members to express their views on the 2018 Policy Address, and take part in different consultation sessions held by the Government to help facilitate the advancement of pharmacy practice.

We all believe that, little by little, we can make a difference!

Public Education on Health and Drug Safety Never Ends

Counterfeit medicines is a serious public health issue. In view of the growing threat from counterfeit medicines posing to Hong Kong citizens, a joint press conference was held by the Society and the Centre for Safe Medication Practice and Research (CSMPR) of the University of Hong Kong on 17th July 2018, to raise public awareness of counterfeit medicines in the city. Useful practical tips for identifying safe medicines were discussed at the press conference and general public were advised not to buy medicines from unknown sources.

A joint press conference was held by the Society and the Centre for Safe Medication Practice and Research (CSMPR) of the University of Hong Kong on 17th July 2018.

More Seminars and Symposiums Coming Soon

In the coming months, SHPHK will organise a series of seminars and symposiums on a wide range of topics, including chemotherapy-induced nausea and vomiting, chronic heart failure, multiple myeloma, biosimilars and more!

Furthermore, there will be some educational events co-organised by the Society and the Pharmacy Central Continuing Education Committee (PCCC) in the future. Members are highly encouraged to attend those events to meet pharmacists of different sectors to exchange ideas and share experience with colleagues and other healthcare professionals. Watch this space!

If you would like to get involved in the activities organized by SHPHK, feel free to join us as member to enjoy the benefits of the Society, and work with us to promote the betterment of the pharmacy profession together!

You are most welcome to follow the Society's Facebook page (@SHPHK) to know more about the Society's development and activities. You may also visit the Drug Education Resources Centre (DERC) Website: www.derc.org.hk to keep abreast of the latest news and development of drugs in Hong Kong. Join us now as new member or to renew your membership at the Society's website: www.shphk.org.hk.

Prepared by Ivy Chan

Active Ingredient:
Empagliflozin and linagliptin

Presentation:
Pale pink, arc triangular, flat faced, bevel-edged, film-coated tablets.
Each film-coated tablet contains 25mg empagliflozin and 5mg linagliptin.
Each film-coated tablet contains 10mg empagliflozin and 5mg linagliptin.

Pharmacological Properties:
Glyxambi combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: empagliflozin, a sodium-glucose co-transporter (SGLT2) inhibitor, and linagliptin, Dipeptidyl-Peptidase-4 (DPP-4) inhibitor.

Empagliflozin is a reversible, highly potent (IC50 of 1.3nmol) and selective competitive inhibitor of SGLT2. Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5,000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut.

Linagliptin is an inhibitor of the enzyme DPP-4, an enzyme which is involved in the degradation of incretin hormones glucagon-like-peptide-1 (GLP-1) and glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide (GIP). These hormones are rapidly degraded by the enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels.

Indications:
Glyxambi, fixed dose combination of empagliflozin and linagliptin, is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- to improve glycaemic control when metformin and/or sulphonylurea and one of the mono-components of Glyxambi do not provide adequate glycaemic control
- when already being treated with the free combination of empagliflozin and linagliptin

Dosage & Administration:
The recommended starting dose is 1 film-coated tablet of Glyxambi 10mg/5 mg once daily.
In patients who tolerate this starting dose and require additional glycaemic control, the dose can be increased to 1 film-coated tablet of Glyxambi 25mg/5mg once daily.
When Glyxambi is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia.
Patients switching from empagliflozin (either 10mg or 25mg daily dose) and linagliptin (5mg daily dose) to Glyxambi should receive the same daily dose of empagliflozin and linagliptin in the fixed dose combination as in separate tablets. The metformin dose should be continued.

Contraindications:
Hypersensitivity to the active substances, to any other SGLT2 inhibitor, to any other DPP-4 inhibitor, or to any of the excipients.

Precautions:
Glyxambi should not be used in patients with type 1 diabetes.
Diabetic ketoacidosis (DKA)
Use with medicinal products known to cause hypoglycaemia
Acute pancreatitis
Monitoring of renal function
Use in patients with renal impairment
Use in patients at risk for volume depletion
Urinary tract infections
Lower limb amputations
Hepatic injury
Cardiac failure
Urine laboratory assessments
Elevated haematocrit
Bullous pemphigoid
Effects on ability to drive and use machinery
Use in elderly

Drug Interactions:
<u>Insulin and sulphonyluretas</u>
Insulin and sulphonylureas may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or sulphonylureas may be required to reduce the risk of hypoglycaemia when used in combination with Glyxambi.

Diuretics

Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Effects of other medicinal products on empagliflozin

Empagliflozin is mainly excreted unchanged. A minor fraction is metabolised via uridine 5'-diphosphoglucuronosyltransferases (UGT); therefore, a clinically relevant effect of UGT inhibitors on empagliflozin is not expected. The effect of UGT induction on empagliflozin has not been studied. Co-administration with known inducers of UGT enzymes should be avoided because of a risk of decreased efficacy of empagliflozin. Co-administration of empagliflozin with probenecid, an inhibitor of UGT enzymes and OAT3, resulted in a 26% increase in peak empagliflozin plasma concentrations (Cmax) and a 53% increase in area under the concentration-time curve (AUC). These changes were not considered to be clinically meaningful. An interaction study with gemfibrozil, an in vitro inhibitor of OAT3 and OATP1B1/1B3 transporters, showed that empagliflozin Cmax increased by 15% and AUC increased by 59% following co- administration. These changes were not considered to be clinically meaningful. Inhibition of OATP1B1/1B3 transporters by co-administration with rifampicin resulted in a 75% increase in Cmax and a 35% increase in AUC of empagliflozin. These changes were not considered to be clinically meaningful. Interaction studies suggest that the pharmacokinetics of empagliflozin were not influenced by coadministration with metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide and hydrochlorothiazide.

Effects of empagliflozin on other medicinal products

Interaction studies conducted in healthy volunteers suggest that empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, diuretics and oral contraceptives.

Effects of other medicinal products on linagliptin

Co-administration of rifampicin decreased linagliptin exposure by 40%, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-glycoprotein (P-gp) or cytochrome P450 (CYP) isozyme CYP3A4 inducer, particularly if these are administered longterm. Co-administration with other potent inducers of P-gp and CYP3A4, such as carbamazepine, phenobarbital and phenytoin, has not been studied. Co-administration of a single 5mg oral dose of linagliptin and multiple 200mg oral doses of ritonavir, a potent inhibitor of P-gp and CYP3A4, increased the AUC and Cmax of linagliptin approximately twofold and threefold, respectively. The unbound concentrations, which are usually less than 1% at the therapeutic dose of linagliptin, were increased 4 to 5-fold after co-administration with ritonavir. Simulations of steady-state plasma concentrations of linagliptin with and without ritonavir indicated that the increase in exposure will be not associated with an increased accumulation. These changes in linagliptin pharmacokinetics were not considered to be clinically relevant. Therefore, clinically relevant interactions would not be expected with other P-gp/CYP3A4 inhibitors. Interaction studies conducted in healthy volunteers suggest that the pharmacokinetics of linagliptin were not influenced by co-administration with metformin and glibenclamide.

Effects of linagliptin on other medicinal products

Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes. Linagliptin is a P-gp substrate, and inhibits P-gp mediated transport of digoxin with low potency. Linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, pioglitazone, warfarin, digoxin, empagliflozin or oral contraceptives providing in vivo evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter (OCT).

Adverse Reactions:

The most frequent adverse reaction was urinary tract infection (7.5% with Glyxambi 10mg empagliflozin/5mg linagliptin and 8.5% with Glyxambi 25mg empagliflozin/5mg linagliptin). The most serious adverse reactions were ketoacidosis (<0.1%), pancreatitis (0.2%), hypersensitivity (0.6%), and hypoglycaemia (2.4%).

Common Adverse Reactions

Urinary tract infection
Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections
Nasopharyngitis
Hypoglycaemia (when used with sulphonylurea or insulin)
Thirst
Cough
Pruritus
Rash
Increased urination
Dysurial
Increased amylase
Increased lipase

Forensic Classification:

P1S1S3