HONG KONG PHARMACEUTICAL JOURNAL

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News & Short Communications

Creating an Eco-Friendly Pharmaceutical Industry: Source Control and Proper Waste Management

Recent Development of Lipid Management: PCSK9 Inhibitors and Inclisiran (2 CE Units)

SHPHK

PSHK

Leqvio (NOVARTIS)

JARDIANCE (Boehringer Ingelheim)

Hong Kong Pharmaceutical Journal: For Detailed Instructions for Authors

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References: 1. Curling J, Goss N, Bertolini J. The History and Development of the Plasma Protein Fractionation Industry. In: Bertolini J, Goss N, Curling J, editors. Production of Plasma Proteins for Therapeutic Use. 1st ed. Hoboken, NJ (United States): John Wiley & Sons, Inc.; c2013. p. 3-28. **2.** Kim J. Introducing Takeda's Plasma-Derived Therapies Business [Internet]. Covington, GA (United States): Takeda Pharmaceutical Company Limited; 2019 Nov 15. Available at: https://www.takeda.com/4ab4df/siteassets/system/investors/report/quarterlyannouncements/fy2019/pdt_20191115.pdf. Accessed 2021 Jun 15. **3.** Quality Standards of Excellence, Assurance and Leadership (QSEAL) [Internet]. Annapolis, MD (United States): Plasma Protein Therapeutics Association; c2020. Available at: https://www.pptaglobal.org/safety-quality/standards/qseal. Accessed 2021 Jun 15. **4.** International Quality Plasma Program (IQPP) [Internet]. Annapolis, MD (United States): Plasma Protein Therapeutics Association; c2020. Available at: https://www.pptaglobal.org/safety-quality/standards/iqpp. Accessed 2021 Jun 15. **5.** Data on file. C-APROM/INT//2144, Plasma-Derived Therapeutics Pathogen Safety Monograph, 2018 Sep. Takeda Pharmaceutical Company Limited.

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

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- Primary Care
- OTC & Health
- Pharmaceutical Techniques & Technology
- Medication Safety
- Herbal Medicines & Nutraceuticals
- Society Activities
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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.

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

Editorial

LAM, May **5**

News & Short Communications

Early Initiation of Oral Molnupiravir Reduced Risk of Hospitalization or Death in At-Risk, Unvaccinated Adults with COVID-19 **6**

Prolonged Survival Observed with Cemiplimab in Recurrent or Metastatic Cervical Cancer **6**

Trastuzumab Emtansine in HER2-positive Metastatic Breast Cancer **6**

Pharmacy Education & Practice

Creating an Eco-Friendly Pharmaceutical Industry: Source Control and Proper Waste Management **7**
LEE, Timothy Pak Hei; CHONG, Donald Wing Kit

Drugs & Therapeutics

Recent Development of Lipid Management: PCSK9 Inhibitors and Inclisiran *(2 CE Units)* **14**
CHU, Lap Ting; HUNG, Wing Lam; KUNG, Shuk Yi; LAM, Wing Sum Tiffany; LI, Wai Yin; LUI, Tsz Yan; MAK, Ho Kin Ivan; LIU, Man Tim Timothy; SUN, Wai Yan Kiwi

Society Activities

SHPHK **23**

PSHK **24**

New Product

Leqvio (NOVARTIS) **25**

JARDIANCE (Boehringer Ingelheim) **25**

Aims and Scope of the Journal

Hong Kong Pharmaceutical Journal: For Detailed Instructions for Authors **27**

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Programme Code: HS073A

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- Higher Diploma in Pharmaceutical Technology (Western Medicine)/ Dispensing Studies/ Pharmaceutical Science/ Hospital Dispensing Studies (HKIVE); or
- Higher Diploma in Pharmaceutical Dispensing (CBCC)

UNIVERSITY OF WOLVERHAMPTON

Application Code: 2050-HS072A
Programme Code: HS072A

Application Deadline: 30 June 2022

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Programme Features:

This programme covers areas of study in life sciences, chemistry and pharmaceutical science. Graduates of this programme may apply for admission to pharmacy programmes in the UK, Australia and New Zealand. Graduates may also apply for admission to various programmes offered by the University of Manchester, U.K. Some exemptions may be granted by those overseas Universities, including the University of Manchester, University of Queensland, Queensland University of Technology, University of South Australia and La Trobe University. Graduates can also apply to the BSc (Hons) Pharmaceutical Science programme, being run by HKU SPACE in collaboration with the University of Wolverhampto.

Entry Requirements:

- have gained Grade E/ Level 2 in HKALE in Chemistry and HKCEE in English Language (Syllabus B), Biology, Chemistry and Mathematics or equivalent;or
- have attained HKDSE Examination Level 2 in five subjects including English and Mathematics, and Chemistry or Combined Science (with Chemistry as one of the component); and have taken Biology or Combined Science (with Biology); or
- hold an Advanced Certificate or Certificate in Pharmacology and Pharmaceutical Administration subject to an overall grade requirement in the certificate with passes in HKCEE English (Syllabus B), Biology, Chemistry and Mathematics; or HKDSE Level 2 in English, Mathematics, Biology and Chemistry (or Combined Science (Chemistry and Biology)); or
- hold a Certificate in Dispensing Studies with a pass in HKCEE Chemistry and 1-year working experience; or
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* These are exempted courses under the Non-Local Higher and Professional Education (Regulation) Ordinance. It is a matter of discretion for individual employers to recognize any qualification to which these courses may lead.

Breakthrough therapies of COVID-19 and hypercholesterolemia

Hong Kong has been hit hard by the COVID-19 fifth wave. Over one million people has been infected and over 9000 lives have been claimed by the virus[1]. Among all the deceased, 96% happened in people ages 60 and older[1] and majority of this group of people were unvaccinated. Contrary to the 78% of people ages 12 years and older who had received at least two doses of the vaccine, less than 20% of people ages 60 and older were vaccinated[1]. Being part of the healthcare team, we should encourage this group of people to be vaccinated as vaccination still remains the best way to prevent COVID-19 infection, severe disease or death.

The introduction of nirmatrelvir/ritonavir and molnupiravir to treat high-risk COVID-19 patients with mild to moderate symptoms may provide a breakthrough in the fight against COVID-19. Although both medications are effective in reducing the risk of hospitalization and death, differences exist between them and pharmacist should be able to make appropriate recommendations accordingly. The SHPHK Webinar on "Clinical consideration of using oral antiviral therapy for symptomatic mild to moderate COVID-19 cases" (page 23) was held with perfect timing to provide essential information for pharmacists.

In this issue, an article by LEE, Timothy Pak Hei and CHONG, Donald Wing-Kit (page 7) discusses how pharmaceuticals enter the ecosystem and their impact on the environment. An interesting case mentioned in the article is the rapid decline of vultures' population in South Asia. Post-mortem examination revealed these vultures suffered from non-steroidal anti-inflammatory drug-induced acute kidney injury and was probably due to the scavenging on dead cattle that were exposed to diclofenac. This is a notable yet tragic example of how pharmaceuticals can pass along the food chains and inflict damage to the entire food web. Moreover, an overview on practice to optimize pharmaceutical supply and waste handling by different countries is provided. In addition, it also explores various approaches for pharmaceutical industry to be more eco-friendly and examines the feasibility of implementing solutions in the pharmaceutical distribution chain.

As mentioned in the article by Chu et al (page 14), many Hong Kong citizens suffer from hypercholesterolemia and the use of low-density lipoprotein cholesterol (LDL-C) lowering agents are on great demand. Although statins have been used as the first-line treatment, some patients may still be unable to achieve target LDL-C levels with maximum tolerated dose. The introduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have provided another treatment option. PCSK9 inhibitors target the degradation of LDL-C and have proved to improve cardiovascular outcomes in patients with established atherosclerotic cardiovascular disease. Currently, alirocumab and evolocumab are the PCSK9 inhibitors that are available in Hong Kong. The indications, mechanisms of action, efficacy and safety are discussed in this article. In addition, a novel lipid lowering agent, inclisiran, is also included in this review article with an overview of clinical trials that evaluate inclisiran.

I hope you enjoy reading this issue. As always, you may provide suggestions and give feedbacks on any aspect of the Journal by contacting me or other members of the Editorial Committee.

May PS Lam
Editor-in-Chief
03 May 2022

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Prepared by Branson Fok and Chloe Ip

Early Initiation of Oral Molnupiravir Reduced Risk of Hospitalization or Death in At-Risk, Unvaccinated Adults with COVID-19

Date: Feb 10, 2022

Molnupiravir is an oral, small-molecule antiviral prodrug of N-hydroxycytidine (NHC), that is active against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Phase 3 of MOVe-OUT is a double-blinded, parallel-group, randomized, placebo-controlled trial evaluating the safety and efficacy of molnupiravir. Nonhospitalized, unvaccinated adults with mild-to-moderate COVID-19 who had at least one risk factor for progression to severe illness were randomly assigned in a 1:1 ratio to receive either molnupiravir (800 mg delivered as four 200-mg capsules) or placebo, administered orally twice daily for 5 days.

The primary efficacy end point was the incidence of hospitalization for any cause (defined as ≥24 hours of acute care in a hospital or similar facility) or death through day 29 in the modified intention-to-treat population. The primary safety end point was the incidence of adverse events. The interim analysis included 775 participants and the all-randomized analysis included 1433 participants. Baseline characteristics were similar in the two groups with the exception of an imbalance in gender.

At the interim analysis, the risk of hospitalization for any cause or death through day 29 was lower with molnupiravir (7.3% [28 of 385]) than with the placebo (14.1% [53 of 377]) group (difference, −6.8 percentage points; 95% confidence interval [CI], −11.3 to −2.4; P=0.001). Similarly, the all-randomized analysis showed lower percentage of hospitalization or death through day 29 in the molnupiravir than in the placebo group (6.8% [48 of 709] vs. 9.7% [68 of 699]; difference, −3.0 percentage points; 95% CI, −5.9 to −0.1). Adverse events were reported in 30.4% (216 of 710) and 33.0% (231 of 701) of the molnupiravir and in the placebo group respectively.

In conclusion, the initiation of molnupiravir within 5 days after onset of symptoms reduced the risk of hospitalization for any cause or death in at-risk, unvaccinated adults with COVID-19, without posing evident safety concerns.

Source: www.nejm.org

Prolonged Survival Observed with Cemiplimab in Recurrent or Metastatic Cervical Cancer

Date: Feb 10, 2022

Overall survival rate of cervical cancer was concerning with approximately 600,000 new cases and 350,000 deaths occurring worldwide each year. Progression after first-line chemotherapy were common and yet other treatment options were limited. Preliminary clinical trial showed improvements in survival rate with Cemiplimab, a humanized programmed cell death 1 (PD-1) antibody and has been approved for lung and skin cancers.

This open-label, multicentre, phase 3 trial recruited 608 female with a median age of 51 years to randomly receive 350 mg intravenous cemiplimab or placebo every 21 days for up to 96 weeks. Inclusion criteria of the study population are recurrence or metastatic cervical carcinoma after platinum-containing therapy, previous bevacizumab and paclitaxel therapy but discontinued before enrolment and normal renal, hepatic and bone marrow function. Patients received pelvic exenteration were excluded.

Significantly longer median overall survival was observed in the cemiplimab group comparing to the chemotherapy group (12.0 months vs. 8.5 months) with hazard ratio for death of 0.69 (95% confidence interval [CI], 0.56 to 0.84; two-sided P<0.001) and for disease progression of 0.75 (95% CI, 0.63 to 0.89; two-sided P<0.001). Both subgroups of squamous-cell carcinoma and adenocarcinoma showed similar overall survival benefit. Objective response occurred in 16.4% (95% CI, 12.5 to 21.1) and 6.3% (95% CI, 3.8 to 9.6) of the patients treated with cemiplimab and chemotherapy respectively. Grade 3 or higher adverse events were reported in 45.0% of the cemiplimab group and 53.4% of the chemotherapy group. Anaemia (12.0% with cemiplimab and 26.9% with chemotherapy), urinary tract infection (5.0% and 2.8%), and neutropenia (1.0% and 9.0%) were the most common adverse events.

The study provided evidence that cemiplimab may extend the overall survival in patients with recurrent or metastatic cervical cancer after first-line platinum-containing chemotherapy in contrast to single-agent chemotherapy.

Source: www.nejm.org

Trastuzumab Emtansine in HER2-positive Metastatic Breast Cancer

Date: Mar 24, 2022

Trastuzumab emtansine is the standard second-line treatment for patients with human epidermal growth factor receptor 2 (HER2) positive breast cancer. Trastuzumab deruxtecan is approved for HER2-positive metastatic breast cancer patients who have received two or more previous anti-HER2 antibody-based regimens, but the benefits as a second-line therapy have yet been established.

DESTINY-Breast03 is a phase 3, multicenter, open-label, randomized, controlled trial that evaluated the safety and efficacy of trastuzumab deruxtecan as compared with trastuzumab emtansine. The study recruited patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane. The primary end point was progression-free survival with secondary end points including overall survival, objective response, and safety.

A total of 524 patients were enrolled at 169 centers in 15 countries and randomly assigned in a 1:1 ratio to receive 5.4 mg/kg trastuzumab deruxtecan (261) or 3.6 mg/kg trastuzumab emtansine (263) intravenously every 3 weeks. Doses were based on body weight. Baseline characteristics were similar in both groups.

At 12 months, the percentage of patients who were alive without disease progression was 75.8% (95% CI, 69.8 to 80.7) with trastuzumab deruxtecan and 34.1% (95% CI, 27.7 to 40.5) with trastuzumab emtansine (hazard ratio, 0.28; 95% CI, 0.22 to 0.37; P<0.001). Complete or partial response occurred in 79.7% (95% CI, 74.3 to 84.4) and 34.2% (95% CI, 28.5 to 40.3) of patients who received trastuzumab deruxtecan and trastuzumab emtansine respectively. The incidence of adverse events of any grade was 98.1% and 86.6% (grade 3 or 4 was 45.1% and 39.8% respectively). Adjudicated interstitial lung disease or pneumonitis occurred in 10.5% compared to 1.9%; none were of grade 4 or 5 severity.

This trial showed the superiority of trastuzumab deruxtecan over trastuzumab emtansine in reducing the risk of progression or death in patients with HER2-positive metastatic breast cancer who were previously treated with trastuzumab and a taxane. However, trastuzumab deruxtecan was associated to more incidence of adverse events, adjudicated interstitial lung disease and pneumonitis.

Source: www.nejm.org

Creating an Eco-Friendly Pharmaceutical Industry: Source Control and Proper Waste Management

LEE, Timothy Pak Hei[a]; CHONG, Donald Wing Kit[a]*

*[a] GSK (Consumer Healthcare) HK Limited, 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong SAR, China (*Corresponding author)*

ABSTRACT

While pharmaceuticals have established roles in managing diseases, there has been growing concern on how they can be detrimental to our environment. The impact of pharmaceuticals can be reduced by minimising waste at source or proper disposal of pharmaceutical waste. Lately, as a consequence of the COVID-19 pandemic, drug supply interruptions have led to shortages in medicines, sparking conversations on medication re-use and optimisation of drug supply. This article discusses various approaches for different sectors of the pharmaceutical industry to be more eco-friendly and explores the feasibility of implementing solutions already adopted overseas in the pharmaceutical distribution chain.

Keywords: *pharmaceutical waste, waste management strategies, environmental protection*

INTRODUCTION

A 2019 research study found that the pharmaceutical industry generated 50% more emissions compared to the automotive industry.[1] With environmental protection becoming an overarching mission of all industries in the 21st century, the ecological footprints contributed by pharmaceuticals and the pharmaceutical industry collectively are being scrutinised. Most notably, pharmaceutical waste, defined by the World Health Organization (WHO) as "medications and vaccines that have expired, are unused or are contaminated", contribute to negative environmental impacts.[2] Injudicious disposal of pharmaceutical waste introduces medications to aquatic ecosystems, surface waters and groundwater reserves.

ECOLOGICAL IMPACT OF PHARMACEUTICAL WASTE

Ecological Toxicity of Medications

There are more ways for pharmaceuticals to enter our eco-system than we can imagine, as summarised in **Figure 1**. Walking through the typical life cycle of pharmaceuticals, wastes are generated as early as in manufacturing plants, which produces by-products, contaminated solvents and air pollutants as part of the synthetic process of active pharmaceutical ingredients (APIs).[3] Before dispatch, medications are packaged in primary and secondary packaging, which are predominantly plastics due to the durability they provide to protect pharmaceuticals during transportation. Medicines are then delivered to end-users including

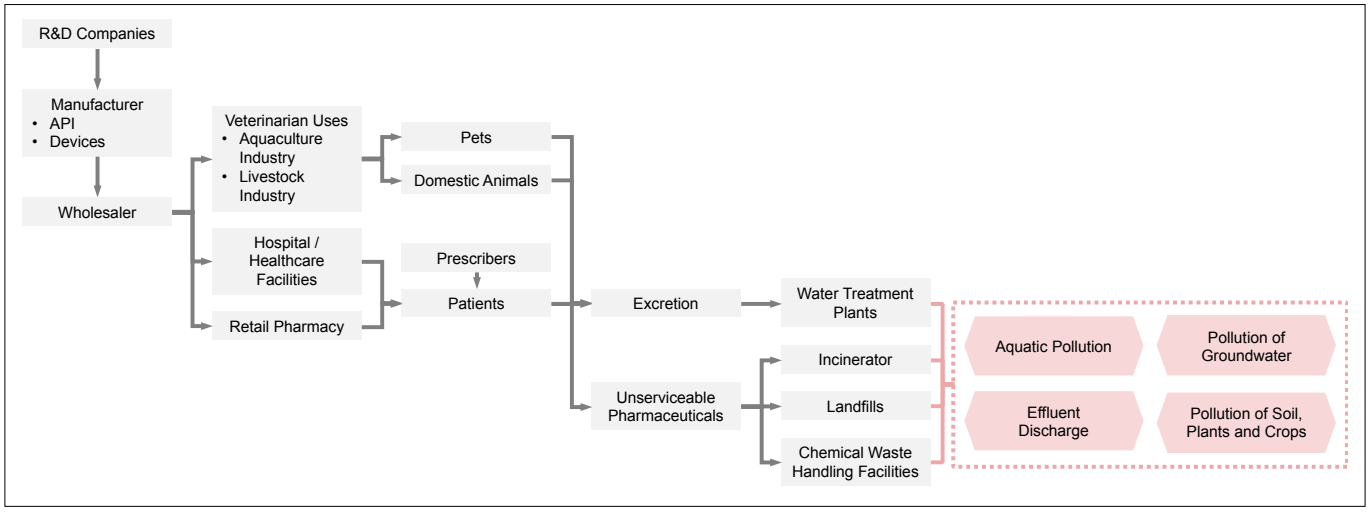

Figure 1*: Pharmaceutical Distribution Chain and Pathways by which Pharmaceuticals Enter the Environment, adapted from*[55]

households, healthcare facilities, and livestock operations. Pharmaceuticals, consumed by both animals and humans, are eliminated from the systemic circulation, and excreted into the environment via wastewater, solid waste disposal, landfills and incineration.

Manufacturing sites of pharmaceuticals inevitably generate effluents that introduce pharmaceuticals to the ecological system. Assay of effluents of wastewater treatment plants responsible for handling wastes generated by pharmaceutical manufacturers detected substantial levels of pharmaceuticals. Effluents collected near sites with pharmaceutical waste discharge contained up to 3000-fold higher concentration of fluconazole compared to sites not at the vicinity of pharmaceutical manufacturing plants.[4] While wastewater treatment facilities remove some medications before discharge, removal rates are highly dependent on the physicochemical properties of the API.[5] For instance, antibiotics are detected in nanomolar to low micromolar concentrations in sewage of sewage treatment plants in Hong Kong.[6] Once pharmaceuticals enter the environment, they undergo degradation which generally reduces their potency. The rate of degradation depends on environmental conditions and chemical properties of the API.

One notable example of environmental dangers posed by medications is the effect diclofenac has on vultures. With medications introduced to the environment as contaminants, they may accumulate and be passed along food chains, inflicting damage to the entire food web. In 2004, a series of vulture deaths in Pakistan was reported to be the result of medications. As the vultures fed on dead cattle which were treated with diclofenac, the vultures were exposed to elevated levels of the non-steroidal anti-inflammatory drug. Post-mortem analysis revealed high diclofenac concentrations sufficient to cause acute kidney injury in the vultures.[7] Fast forward to 2016, the compound aceclofenac is found to be rapidly converted to diclofenac in livestock.[8] This discovery prompted the Government of Bangladesh, India, Nepal and Pakistan to jointly sign a blueprint banning the use of aceclofenac for veterinary purposes as part of the conservative efforts paid to prevent endangered vulture species from extinction.[9] This ecological disaster warned us of the potential impact pharmaceutical contaminants can create when they are inappropriately introduced to the environment. As humans consume animal products, the contaminants can accumulate up the food chain and detrimentally affect our health.

To explore the ecological impact of medications, we shall expand the discussion to agricultural or aquacultural use of medications, especially antimicrobials. The development of antimicrobial resistance (AMR) has been recognised among the top 10 public health threats by the WHO, and there is ample evidence that the overuse and misuse of antimicrobials accelerates the development of AMR. For example, sewage containing broad-spectrum antibiotics may contribute to the spread of extended-spectrum beta-lactamase (ESBL) and carbapenemase-producing bacteria.[10] In Hong Kong, local researchers obtained leachate samples from three landfills, and detected levels of ciprofloxacin, erythromycin and trimethoprim which exceeded the threshold at which the antibiotic is predicted to have no effect in contributing to antimicrobial resistance.[11]

As similar antimicrobials are used to treat infections in both food animals and humans, bacteria resistant to antimicrobials that colonise or infect food animals may be transmitted to humans, further limiting the already-scarce choice of antimicrobials for human use. The Agriculture, Fisheries and Conservation Department (AFCD) has recently released code of practice on proper use of antimicrobials for food animal producers. AFCD recommended livestock farm workers to seek professional advice from a veterinarian before using antimicrobials.[12] If antimicrobials are considered appropriate for treating livestock, antimicrobials on the WHO list of Critically Important Antimicrobials for Human Medicine (WHO CIA list) should be avoided if possible.[13] This approach aims to preserve efficacy of antimicrobials commonly used to treat humans and delay the emergence of AMR.

Apart from antimicrobials, other classes of medications have well-established adverse effects to the environment, summarised in **Table 1**.

Table 1: Notable Medications associated with Undesirable Environmental Consequences

Pressurised metered dose inhalers (pMDIs)	• Chlorofluorocarbon (CFC) propellants are universally substituted by hydrofluoroalkanes (HFAs) after concerns emerged regarding the damage CFCs pose to the ozone layer of the Earth. However, while HFA are ozone-friendly, they still contribute to global warming as they are potent greenhouse gases. • In the United Kingdom, MDIs are responsible for 3.5% of total greenhouse gas emissions from the National Health Service.[14] • To reduce carbon emissions associated with the use of inhalers for respiratory diseases, the British Thoracic Society suggest physicians to consider initiating patients on dry powder inhaler or soft mist inhalers which are propellant-free.[15]
Cytotoxics	• Drugs included in the National Institute of Occupational Safety and Health (NIOSH) list of hazardous drugs were detected in hospital effluents, including cyclophosphamide, ifosfamide and methotrexate, at levels that are significant to aquatic organisms.[16–18]

Despite sporadic reports of medications polluting water systems downstream of pharmaceutical manufacturing plants, our government considers contributions of pharmaceuticals to water pollution minimal, and the Water Supplies Department does not conduct regular surveillance for residual medicines in our drinking water.[19] It has also been suggested that the quantity of unwanted medicines sent for incineration or to landfills is unlikely to pose hazards to the health of the general public.[19] The grave consequences pharmaceuticals can pose on the environment calls attention to proper medication waste management, especially when the ecological impact of pharmaceutical

residues is not precisely quantifiable with limited surveillance programmes in Hong Kong.

OPTIMISING PHARMACEUTICAL SUPPLY AND WASTE HANDLING: PRACTICE AROUND THE WORLD

The complexity of pharmaceutical waste generation provides multiple windows of opportunities to tackle the impending environmental crisis associated with pharmaceutical pollution. Many reasons may lead to wastage of medicines, including changes in therapy, patient recovery before using up the prescribed quantity of medications, non-adherence to therapy due to lack of understanding or adverse effects, and over-prescribing. Medicines may also be left at home when the patient is admitted to healthcare facilities, or if the patient passes away. This section will highlight international practices of pharmaceutical waste handling.

United States

On a federal level, the U.S. Drug Enforcement Administration (DEA) encourages patients to bring their unused over-the-counter and prescription medications to collection programmes.[20] Pharmacy staff are authorised to collect controlled substances from end-users for disposal.[20] DEA also periodically organises National Drug Take Back Day to provide temporary collection sites in the communities for safe drug disposal. The Drug Take Back Days are publicised via public service announcement in the U.S. to advertise the event to the general public.[21]

The U.S. Food and Drug Administration (FDA) outlines appropriate methods of discarding unused medications. The FDA "flush list", provided in **Table 2**, identifies 15 APIs, many of which are opioids, that can be flushed down the toilet if patients were dispensed excess quantities.[22] These medicines are prone to diversion and proven to be fatal if ingested accidentally by children or pets. For instance, fentanyl transdermal release preparations contain a considerable amount of fentanyl even after transdermal application. Prior research was conducted to evaluate the environmental impact posed by flushing the 15 APIs and concluded that there is negligible risk.[23] All medications not on the "flush list" should be disposed at a drug take back site, which may be permanent take-back kiosks within hospitals, community pharmacies, temporary take-back sites in the community, or via mail back programmes. If disposal via a drug collection point is impractical, medications not on the flush list can be mixed with unpalatable substances like coffee ground, and discarded within a plastic ziplocked bag together with household waste.[24]

As of August 2021, 38 states and Guam enacted laws to provide additional safeguard for proper drug disposal. Twenty-one states have operating drug recycling programmes in the United States. The operations of drug donation and drug reuse programmes across the United States vary between states. Differences lie in the types of medications accepted for reuse, eligibility of drug donors, sources of funding and protocols for handling donated drugs. For more detailed comparison in drug repository programmes on a State level, please refer to the position statement by the American Society of Clinical Oncology and an extensive review by Briones.[25,26]

Table 2: FDA List of Active Pharmaceutical Ingredients that should be Flushed[22,23]

- Buprenorphine
- Diazepam rectal gel
- Fentanyl
- Hydrocodone (benzhydrocodone)
- Hydromorphone
- Meperidine
- Methadone
- Methylphenidate transdermal system
- Morphine
- Naloxone, naltrexone (listed due to combination with buprenorphine, oxycodone, morphine)
- Oxycodone
- Oxymorphone
- Sodium oxybate
- Tapentadol

Community pharmacists in the United States are obliged to provide patient education and maintain drug collection sites for patients to return their unused medications. To educate the public on pharmaceutical waste disposal, the Texas State Board of Pharmacy required medications to be labelled with the statement "Do not flush unused medications or pour down a sink or drain".[27] In addition, a written notice instructing patients to safely dispose of their controlled substance medications via collection points or at-home disposal methods must be provided at the time of dispensing.[28] To minimise impact of drug disposal to the environment, community pharmacies partner with companies who generate solutions to deactivate medications before patients discard them. Patented drug disposal systems such as DisposeRx® and Deterra® employs polymers and activated carbon, respectively, to neutralise medications when water is added to the proprietary disposal pouches.[29–31] Retail pharmacy chains including Walmart, Walgreens and CVS partnered with DisposeRx® to offer at-home drug disposal solutions in stores without a designated medication collection kiosk.[32–34]

Non-profit organisations also play a role in the redistribution of medications to those in need. The Supporting Initiatives to Redistribute Unused Medicine (SIRUM) is a social enterprise that collects surplus, unused and yet-to-expire medications, and redistributes them to those who cannot afford their medications. Since 2011, SIRUM has redistributed over 100 million USD worth of medications and donated over 1 million prescriptions to eligible individuals.[35] This initiative provided affordable medications for patients who have difficulty paying out-of-pocket charges.

European Union (EU)

Most member states of EU have comprehensive drug waste collection schemes, mostly led by community pharmacies to facilitate disposal of unused drugs.[36] One successful example of drug redistribution programme is the GIVMED programme operating in Greece. GIVMED was founded in 2016, focusing on reducing medicinal waste and improving patient access to medicines. The GIVMED service starts with a mobile application that allows the public to log their excess medications by scanning the barcode on the outer packaging. GIVMED keeps track of the quantities of medications, and allow institutions such as government-funded pharmacies to re-distribute the excess medications to those in need. Pharmacists are recruited to examine whether collected medications are in good quality.

United Kingdom

Previously, reuse or recycling of medications was not recommended by British authorities as it is impossible to guaranteed that the quality of medicines is maintained after they are dispensed to patients. Since 2020, the coronavirus pandemic has exerted additional strain on the pharmaceutical supply chain, causing delays in drug delivery to pharmacies worldwide. At the start of the pandemic, NHS issued guidance for reusing medications in hospice care and care homes, which are healthcare institutions where proper medication storage is ensured. Unused medicines that would normally be disposed of will be reused on other patients if consent is given by the patient or their carer.[37]

Local Practice of Pharmaceutical Waste Handling

Institutions

In Hong Kong, the management and disposal of pharmaceutical waste is governed by the Waste Disposal Ordinance (Cap. 354) as well as the Waste Disposal (Chemical Waste) (General) Regulation (Cap. 354C). Expired or unserviceable medication waste are classified as chemical waste in the setting of healthcare institutions or clinics. Institutions that generate chemical waste are required to register as a chemical waste producer with the Environmental Protection Department (EPD). Each disposal of unserviceable medication should be approved by EPD, and waste should be sent to the chemical waste treatment centre as the designated disposal point.[38,39] Unlike in the United States or Canada, local community pharmacies do not serve as drug waste collection points, nor will they collect surplus medications from consumers.

Patients

While the disposal of medication waste from healthcare institutions must follow Cap. 354 and Cap. 354C, the disposal of such wastes from households do not fall within the scope of the Ordinance. As of 2017, the Hong Kong government has no plans to initiate services for collecting residual medicines from the general public.[19] The lack of policy support and infrastructure encouraging the public to properly dispose of their leftover medications has contributed to improper household pharmaceutical waste handling. A significant lack of awareness is demonstrated among the elderly. In 2020, The Elderly Rights League (Hong Kong) surveyed 66 elders residing in Sham Shui Po, Kwun Tong and Wong Tai Sin districts on their experience with taking medications.[40] A mere 4.5% responded that they do not have leftover medications at home. When asked about how they handle leftover medications, over 80% hoarded them at home in case they need it in the future, and 6.3% will gift their medications to others. Ample evidence also suggests that non-adherence is a common issue, generating large quantities of excess drug waste.[41–43] Together, this data has exposed the inadequacies in pharmaceutical waste handling education in Hong Kong.

SOLUTIONS TOWARDS ECO-FRIENDLY PHARMA

Taking together exemplary overseas examples and gaps identified in the local setting, a multi-faceted approach should be adopted to improve sustainability and environmental friendliness of the pharmaceutical industry. **Table 3** provides a summary of potential actions various stakeholders can initiate to minimise the environmental impact of medications.

Minimise Medication Wastage: Highlighting the Role of Pharmacists

Means of proper medication waste management should be introduced to the public through education campaigns, targeting the elderly as they are most prone to frequent changes in drug regimen, contributing to drug wastage from discontinued medications. Similar to the practice in the United States, the proper way for disposing medications should be incorporated in pharmacist-patient conversations to ensure proper disposal practice. A 6-month study conducted in Romania selected 5 community pharmacies as pilot test sites for a public education campaign regarding medication waste management. The Romanian public was very responsive to the campaign, as reflected by a significant boost in proportion of individuals who were willing to return expired or unused medications to the community pharmacies from 1.1% to 87.3%.[45] This affirmed the role pharmacists can play to optimise unused medication disposal, in turn minimising the impact of pharmaceuticals on the environment. However, awareness does not always translate to behavioural changes. Proper means of drug disposal (such as drug collection kiosks) must be made readily accessible to the public. Convenient local drug take-back options should be provided to ensure that patients will safely discard leftover drugs.

Hospital pharmacists can also introduce initiatives to reduce medication waste. Medications dosed by weight or body surface area are major contributors toward drug wastage. Antineoplastics with highly variable, patient-specific dosages are prone to wastage because they often only come in fixed dose vials. The leftover portion of the dose will likely be discarded or used to make up

Table 3: Potential Measures to Optimise the Management of Pharmaceutical Waste		
Players	Source Control	Proper Waste Handling
Government	• Conduct routine surveillance on leachate of landfills / water reserves, testing for medications present in the drinking water supply and groundwater systems. • Enact policies mandating the return of unused medications to designated drug collection points in the community.	• Educate the public on how to handle domestic pharmaceutical wastes. • Roll out community drug collection schemes for disposal of household pharmaceutical wastes. • Set up drug distribution services by partnering with NGOs to provide unused but unexpired medications to the underprivileged.
Healthcare Institutions	• Prescribers: control stockpiling of medications by prescribing appropriate amount of medications • Hospital pharmacists: provide pharmacist-led drug refill service to limit prescription duration, evaluate potential cases of medication waste due to non-adherence, and prevent excess quantity of medications being dispensed to patients.[44]	• Identify and reuse medications that are of good quality and were properly stored after dispensing to clinical units / out-patients. • Hospital pharmacies: serve as collection points for unserviceable medications. • Hospital pharmacists: educate patients on proper disposal methods for surplus medications
Community / Outreach Pharmacists working at OAH	• Perform medication reconciliation for clients who receive medications from multiple sources.	• Community pharmacies: initiate drug recycling services to improve patient's access to drug disposal sites for unserviceable medications.
Pharmaceutical Industry	• Adopt green chemistry principles by recovering API lost during drug extraction or synthesis to minimise waste. • Drug product design: for medications with variable dosing e.g. by weight or body service area, introduce multiple vial sizes based on common doses to minimise wastage from excess, leftover portion of reconstituted medications.	

NGO, non-governmental organisations; OAH, old age homes

the dose for another patient, depending on institutional operation guidelines. Dose rounding is a plausible solution to reduce wastage of the unused portion of a vial of medications. The Haematology/Oncology Pharmacy Association (HOPA) suggests that rounding the dose of cytotoxic chemotherapy or biologic agents is acceptable to reduce waste and costs.[46] A study conducted at an oncology clinic estimated over 30,000 USD of saved costs for 70 patients in a 12-month duration by rounding down the dose by up to 10%.[47] In handling parenteral chemotherapy, closed-system transfer devices may be adopted to extend period of sterility of medications in a vial. The PhaSeal system preserves sterility of unpreserved fluorouracil aliquots for up to 14 days, enabling pharmacists to take advantage of the extended beyond-use date to fully utilise the entirety of the vials.[48] Locally, drug reuse has limited role in public healthcare institutions. Hospital Authority has issued internal guidelines on the Reuse of Returned Medicines. Patients' brought-in medicines returned from wards and medicines returned by outpatients are not reused as per Hospital Authority guidance, as the storage conditions and integrity of medications dispensed to patients cannot be ascertained.

Patients can also help to reduce medicine wastage by checking quantities of medications at home, especially for medicines that are prescribed for as needed usage. Patients should avoid stockpiling medications as this can pose a safety risk especially to children who may accidentally ingest medications. If patients have missed taking medications, either intentionally or inadvertently, they should inform their healthcare professionals.

Drug manufacturers should periodically re-evaluate the stability of their products to explore the possibility of extending their shelf-life. In 2019, the U.S. FDA extended the expiration dates of Mylan's generic epinephrine autoinjector by 4 months after carefully reviewing the stability data provided by Pfizer.[49] This decision was made in response to a supply constraint that lead to product shortage in the United States. Regulatory authorities rigorously evaluating shelf-life and stability of medications may consider granting shelf-life extension to medications with a high demand given long-term stability studies are conducted to support such decision. Ultimately, the environmental benefits of reducing waste due to expiry must be weighed against hazards of medications losing their potency to degradation if storage periods are prolonged.

Source Control: Improving Pharmaceutical Packaging

While local drug-reuse programmes are yet to be widely adopted to minimise pharmaceutical waste, reducing waste generation at the source is still of great potential. Waste arises from pharmaceutical packaging, including blister packets which are made from layers of plastic e.g. polyvinyl chloride (PVC) and aluminium foil. Given the complexity of materials used to make medication blisters, they are traditionally rejected by recycling sites and are discarded as household waste. The Australian packaging company Amcor has developed polyethylene (PE)-based blister packaging, aiming at eliminating PVC-based packaging which is known to be challenging to recycle. Its patented AmSky™ material generates 70% less carbon footprint comparing to the conventional PVC-based blisters.[50,51] Aside from reducing environmental

impact at source, packaging materials also have residual value and can be recycled and repurposed for other applications. Teracycle, a company based in the United Kingdom launched a medicine packet recycling programme, which allows pharmacies to set-up drug packet collection sites for end-users to drop off their emptied blister packs. After collection, TerraCycle sort, segregate, clean and process recyclable materials to make them into recycled plastic pellets that can be made into containers, outdoor furniture, or floorings.[52] This programme proved to be a success and is well-received by the public, as evident from the high uptake of medication blister packs from participating pharmacies leading to its temporary suspension due to overload.

Respiratory medicine delivery relies on inhalers, which are major contributors to global warming as discussed before. Boehringer Ingelheim has developed Respimat® re-usable, an improved version of their Respimat® inhaler products. The new-generation inhaler design allows the user to replace cartridges monthly, and only need to be discarded every 6 months. This greatly reduces the number of inhalers patient need per year from 12 to 2.[53] The company estimated a reduction of 776 tonnes of plastic waste and 14300 tonnes of carbon dioxide emissions by 2025 with this initiative.[53] These reusable Respimat® inhalers were added to the Pharmaceutical Benefit Scheme in Australia in 2021 to improve patient access, marking an important step towards sustainable pharmaceuticals.[54] This example illustrates how the pharmaceutical industry should place environmental conservation as one of their goals to demonstrate corporate social responsibility, and attempt to manage pharmaceutical waste along their supply chain.

Another direction pharmaceutical companies can take to protect our environment is to focus on developing packaging designs that allow for continuous monitoring of storage conditions throughout the pharmaceutical supply chain, even after medications are dispensed to consumers. This is because a major barrier to reusing medications worldwide is the uncertainty of quality and safety of medicines returned to pharmacies or institutions. Novel packaging designs allowing healthcare professionals to discern whether medications were stored properly at patient's home would provide a more favourable environment for institutions to re-use medications that are still in date and of reasonable quality.

CONCLUSION

Emerging studies on the environmental consequences of medication use has drawn concern from Green Groups and governments around the world, raising voices to promote sustainable practices in the pharmaceutical industry. Overseas practices of drug waste management, including the United States, the European Union, and the United Kingdom, present strategies that may be considered in Hong Kong to improve the local pharmaceutical waste management standards. Waste stemming from each and every step of the pharmaceutical distribution chain should be addressed, which requires tremendous efforts from corresponding stakeholders through the optimisation of waste handling infrastructures and logistics support, policy-making, and public education. As drug experts, pharmacists are at an advantageous position to educate the public and empower patients to improve medication waste handling. Pharmacists working in different sectors should target different steps of the pharmaceutical distribution process to encourage proper pharmaceutical waste management, ultimately contributing to a greener society.

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Recent Development of Lipid Management: PCSK9 Inhibitors and Inclisiran

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ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been a new treatment option for hyperlipidemia in Hong Kong since 2016. They are preferred in patients with statin intolerance, as a monotherapy or in combination with other lipid-regulating agents. Despite their high efficacy in lowering low-density lipoprotein cholesterol (LDL-C) level, their uses are restricted due to limited safety studies and high cost. A literature review of two PCSK9 inhibitors registered in Hong Kong, namely Alirocumab and Evolocumab, as well as a novel lipid lowering agent, Inclisiran, registered in September 2021 in Hong Kong, are discussed for their indications, mechanisms of action and common adverse effects.

Keywords: *Proprotein convertase subtilisin/kexin type 9 inhibitors, Alirocumab, Evolocumab, Inclisiran, Hypercholesterolemia*

INTRODUCTION

From the Population Health Survey 2014/15 released by the Department of Health, the prevalence of hypercholesterolemia in Hong Kong citizens was 49.5% with a worsening trend over the last 10 years.[1] Antihyperlipidemic drugs are hence on great demand and statins have always been the first-line treatment since the first approval of lovastatin for human use in 1987. They are proven effective in reducing both LDL-C levels and cardiovascular events.[2] Nonetheless, in an appreciable number of patients, the use of statins is inadequate to achieve target LDL-C levels by the maximum tolerated dose. This has developed the need to discover new classes of antihyperlipidemic drugs, such as PCSK9 inhibitors (alirocumab and evolocumab) and a small synthetic interfering RNA (siRNA) molecule (inclisiran).

ALIROCUMAB (Praluent®)

Approved Indications

Alirocumab has been available in Hong Kong as Praluent® since 2016, with a legal classification of P1S1S3.[3] Available forms include prefilled pens and syringes with strengths of 75mg/ml and 150mg/ml.[3] It was first indicated by FDA for adult patients with primary hyperlipidemia including heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who failed to achieve sufficient LDL-C reduction with statin therapy at maximum tolerable dose.[4] In April 2019, it was further approved for the prevention of cardiovascular events, for example, myocardial infarction, stroke, and unstable angina which requires hospital admission.[5] Moreover, it can be used as a monotherapy or co-administered with other lipid-regulating agents such as ezetimibe to further lower LDL-C.[5]

Alirocumab is currently included in the Hospital Authority formulary as a special drug.[6] In March 2019, a reduction of U.S. list price by around 60% to US$5,850 annually (ca. HKD$1,900 per dose) was announced. With a better price and new indications, alirocumab is believed to become a more accessible treatment option to patients.[7]

Mechanism of Action

PCSK9 is an enzyme predominantly produced in the liver. Formation of ligand-receptor complex between PCSK9 and low-density lipoprotein receptors (LDL-R) present on hepatocytes surface triggers LDL-R degradation in the endosomes and lysosomes. Higher plasma LDL-C levels are resulted from degradation of LDL-R, which is responsible for the clearance of LDL in blood circulation. Alirocumab is a human monoclonal antibody that specifically binds to PCSK9 and blocks the binding between the enzyme and LDL-Rs. This allows normal recycling of LDL-R back to hepatic cell surface

with less degradation for clearance of circulatory LDL-C, eventually lowering LDL-C levels.[8]

Evidence from Clinical Studies

Primary Hyperlipidemia:
In ODYSSEY FH I AND FH II studies, a total of 735 patients with HeFH, who had suboptimal LDL-C control by maximum tolerated statins, received alirocumab treatment and showed significant reductions in LDL-C at week 24 (57.9% and 51.4% from baseline versus placebo).[9]

The efficacy of alirocumab is further supported by various clinical trials: ODYSSEY COMBO I study (2015; 316 participants) and ODYSSEY LONG TERM clinical trials (2015; 2341 patients). Alirocumab achieved a significantly greater LDL-C reduction when compared to placebo at week 24, with a difference of 45.9% and 61.9% respectively.[10,11] Besides comparison with placebo, studies also compared alirocumab as an add-on to other lipid-lowering treatment regimens. In ODYSSEY COMBO II randomized controlled trials (2015; with 720 patients), alirocumab showed to reduce LDL-C level by 29.8% more than ezetimibe with a similar safety profile. In ODYSSEY OPTIONS I Randomized Trial (2015), adding alirocumab to atorvastatin presented greater decreases in LDL-C, when compared to using ezetimibe, doubling the statin dose or switching to rosuvastatin.[12,13]

Efficacy and safety of alirocumab as monotherapy was also investigated in the ODYSSEY ALTERNATIVE randomized trial, which included 361 statin-intolerant patients. Alirocumab presented a reduction in LDL-C of 30.4% more than ezetimibe with comparable adverse events and fewer skeletomuscular adverse events than atorvastatin.[14]

Prevention of Cardiovascular Events:
The expanded indication approved by the FDA is based on ODYSSEY OUTCOMES (2018) in 18,924 patients with elevated LDL-C despite statin therapy at maximum tolerated dose and acute coronary syndrome within 1 year of enrolment. The hazard ratio of recurrent cardiovascular events in alirocumab treatment group was 0.85 (95% CI, 0.73 to 0.98) at a median follow-up duration of 2.8 years, when compared to placebo.[15] The post-hoc analysis of ODYSSEY LONG TERM trial (2015) conducted earlier also revealed that the rate of major adverse cardiovascular events was lower with alirocumab than placebo, which coheres with the recent trial.[11]

A later study, ODYSSEY EAST (2019), assessed add-on alirocumab treatment by comparing it with ezetimibe in Asian population (40 Chinese, 17 Indian and 4 Thai). The results were consistent with previous ODYSSEY studies that the major trial population was non-Asian. This further guarantees the efficacy and safety of alirocumab in lipid-lowering treatment in Hong Kong.[16]

Adverse Effects

Deriving results from 9 placebo-controlled trials which included 2476 patients with alirocumab, the most common adverse drug events are nasopharyngitis (11.3%), injection site reactions (7.2%) and influenza (5.7%).[5] Other adverse events include allergic reactions (8.6%) and elevated liver enzymes (2.5%), which are the major causes of discontinuation of treatment in the clinical trials.[5]

The issue of immunogenicity was reported in 1.2% of patients treated with alirocumab. Nevertheless, the efficacy of alirocumab is not lowered in patients who exhibited neutralizing antibodies.[17]

EVOLOCUMAB (Repatha®)

Approved Indications

Evolocumab under the brand name of Repatha® is available in Hong Kong from 2016.[3] It is marketed as 140mg/ml solution for injection in pre-filled syringe and prefilled autoinjector.[3] Both preparations are legally classified as P1S1S3 poison.[3] Evolocumab is approved by both FDA and EMA for reduction of cardiovascular risk with established ASCVD and treatment of primary hyperlipidemia, including HoFH and HeFH, as either a monotherapy or combination therapy with other lipid-lowering therapy.[19,20]

Mechanism of Action

The mechanism of action of evolocumab is almost the same as alirocumab. The only difference between them is that alirocumab is an IgG1 isotype while evolocumab is an IgG2 isotype.[21]

Evidence from Clinical Studies

Reduction of cardiovascular risk in ASCVD patient:

The efficacy and safety of combination therapy of evolocumab and statin were established in FOURIER study (2017), which was a multinational phase 3 randomized and double-blind clinical trial with 27,564 patients. The addition of evolocumab to moderate- or high-intensity statin therapy was more efficacious than statin monotherapy as revealed by 59% reduction of LDL-C levels from baseline compared with the control.[22] Significant reduction in cardiovascular events was demonstrated in the clinical study group without compromised safety profile as compared with placebo.[22] The FOURIER study also highlighted that cardiovascular benefit is consistent in patients with variable baseline LDL-C levels ranging from 1.9 mmol/L to 3.3 mmol/L and persists even when LDL-C level is reduced below targeted range.[22] The efficacy and safety of evolocumab in Asians is proven to be not significantly different from that in non-Asian background patients in the FOURIER

study, supporting the use of evolocumab in Asian patients for reduction of cardiovascular risk without dose adjustment required.[23]

Primary Hyperlipidemia:

There are several clinical studies published in 2014 supporting the efficacy of evolocumab as combination therapy with statin or monotherapy alone. Both LAPLACE-2 (2067 patients)[24] and DESCARTES (905 patients)[25] randomized clinical studies have demonstrated significant reduction in LDL-C levels in patients receiving evolocumab treatment on top of baseline statin therapy regardless of the type, intensity and dose of statin. For the group receiving baseline 10mg or 80mg atorvastatin in LAPLACE-2 study, higher reductions in LDL-C level were observed in patients receiving evolocumab than those receiving ezetimibe in both two weeks or one-month regimen, suggesting that evolocumab is comparable to ezetimibe as add-on therapy to statin.[24] DESCARTES study also supported the efficacy of evolocumab as adjuvant drug treatment to diet alone.[25] The result from a 12-weeks clinical study involving 614 patients, MENDEL-2, presented 39.3% and 37.6% more LDL-C level reduction in patients receiving biweekly and monthly evolocumab monotherapy respectively than those receiving daily ezetimibe monotherapy.[26] The above finding supports that evolocumab is a comparable option to ezetimibe as monotherapy for hyperlipidemic patients who are contraindicated to, intolerant to, or show historically poor response to statins. Long-term efficacy, safety and tolerability of parental evolocumab treatment over 5-years are reinforced by OSLER-1 study.[27]

Homozygous familial hypercholesterolemia:

The 12-week phase 3 study, TESLA study, has affirmed the indication of evolocumab on patients with HoFH. In TESLA, patients receiving evolocumab on top of baseline lipid-lowering therapy demonstrated a decline in LDL-C level by an average of 31% and apolipoprotein B by 23% as compared with placebo, without adjunctive apheresis.[28] The long-term safety and tolerability of evolocumab therapy up to 48 weeks is proven by the TAUSSIG study in 2017.[29] However, clinical evidence on the Asian population is still lacking for confirmation of efficacy and safety of evolocumab administration in the local population.

Adverse Effects

The safety profile of evolocumab is quite similar to that of alirocumab. Deriving results from 8 placebo-controlled trials including 2651 patients treated with evolocumab, the most common adverse drug events include nasopharyngitis (10.5%), upper respiratory tract infection (9.3%), influenza (7.5%), back pain (6.2%) and injection site reactions (5.7%).[20] Meanwhile, myalgia (4.0%) is the most common cause of discontinuation of treatment during the clinical trials.[20]

The correlation between lipid lowering statin therapy and incident diabetes was discussed.[18] Nevertheless, the FOURIER study proved that the risk of new-onset diabetes was not intensified by the administration of evolocumab in both non-diabetic and prediabetic patients at baseline.[30] Moreover, drug neutralizing antibodies to evolocumab were not detected during clinical trials.

USING PCSK9 INHIBITORS IN SPECIAL GROUPS OF PATIENTS

Efficacy:

The efficacies in reducing cardiovascular risk of alirocumab and evolocumab are compared by evaluating ODYSSEY OUTCOMES and FOURIER clinical trials **(Table 1)**. Both trials have recruited cardiovascular disease patients with LDL-C level ≥ 70mg/dL or a non-HDL-C ≥ 100mg/dL, with concurrent use of high-intensity statin therapy.[30,31] The primary endpoint measured in both trials includes the composite of cardiovascular death, unstable angina requiring hospitalization, stroke, myocardial infarction.[30,31] The hazard ratios for alirocumab and evolocumab are 0.85 (alirocumab: 95% CI 0.75 to 0.93 ; evolocumab: 95% CI 0.79 to 0.92), showing both are effective drugs in ASCVD risk reduction during the mean follow-up duration of 2.8 years and 2.2 years, respectively.[30,31]

Although alirocumab and evolocumab were not compared head-to-head in ODYSSEY Alternative and MENDEL-2 studies, both trials recruited patients aged 18 years and above with moderate cardiovascular risk and LDL-C levels ≥ 100mg/dl.[14,26] After administration of 75 mg alirocumab or 140 mg evolocumab every 2 weeks as monotherapy for primary hyperlipidemia, the percentage reductions in LDL-C levels are greater than that of 10mg ezetimibe monotherapy for 31.5% and 39.3% after 12-weeks administration, respectively.[14,26]

Patients with renal or hepatic impairment:

Patients with severe renal impairment exhibited the same therapeutic benefits of evolocumab when compared to those without renal insufficient.[20] Both drugs are not eliminated by the kidneys, thus no dosage adjustment is required in patients with renal impairment.[5,20] Similarly, dose adjustment is proven unnecessarily for patients with mild to moderate hepatic impairment.[5,20]

Pediatric and Pregnancy:

Safety and efficacy on pediatric patients and adolescents have not been established in alirocumab.[5] Nonetheless, limited data of evolocumab on pediatric patients is available. The safety and efficacy of evolocumab have been established in young patients with HoFH aged from 13 to 17 in TESLA clinical trial with result resembling the profiles of adult patients.[20] There is neither data for evolocumab usage on pediatric patients with HoFH aged below 13 nor pediatric patients with HeFH at all ages.[5,20]

Table 1: Practice points of Alirocumab and Evolocumab		
	Alirocumab (Praluent®)	Evolocumab (Repatha®)
Indications[5,20]	Primary Hyperlipidemia Reduce risk of MI, stroke, unstable angina	Primary Hyperlipidemia Reduce risk of MI, stroke, coronary revascularization
Dosage[5,20]	75-150mg SC Q2 weeks or 300mg Q4 weeks	HoFH: 420mg Q4 weeks Others: 140mg Q2 weeks or 420mg Q4 weeks
ASCVD Risk Reduction[31,30]	Harzard ratio: 0.85 (95% CI 0.75-0.93)	Harzard ratio: 0.85 (95% CI 0.79 to 0.92)
Efficacy[32,22]	44-58% reduction in LDL-C	54-61% reduction in LDL-C
HA formulary[6]	✓	✓
Price (US list price)[7,33]	~ HKD$1,900 per dose	~ HKD$1,900 per dose
Renal function[5,20,34]	No dose adjustment for mild/moderate renal impairment No data for severe renal impairment Mild renal impairment: CrCL 50-80 mL/min Moderate renal impairment: CrCL 30-50 mL/min	No dose adjustment for renal impairment
Hepatic function[5,20,35]	No dose adjustment for mild/moderate* hepatic impairment No data for severe hepatic impairment *Mild liver impairment: ALT 1.25-2.5 Moderate liver impairment: 2.5-5.0	No dose adjustment for mild/moderate* hepatic impairment No data for severe hepatic impairment *Mild liver impairment: ALT 1.25-2.5 Moderate liver impairment: 2.5-5.0
Pediatric use[5,20]	Safety and efficacy have not been established	HoFH: safety and efficacy established (13-17 y/o) No data for HeFN/ HoFN (<13 y/o)
Geriatric Use[5,20]	✓	✓
Race[5,20]	No significant difference	No significant difference
Gender[5,20]	No significant difference	No significant difference
Body weight[5,20]	No significant difference	No significant difference (drug concentration decrease with increasing body weight but no dose adjustment required)
Pregnancy[5,20]	No available data	No available data
DDI[5,20]	No clinically significant DDI	No clinically significant DDI
Side effects[5,20]	Nasopharyngitis, hypersensitivity reactions, influenza, urinary tract infection, diarrhea, liver enzyme abnormalities	Nasopharyngitis, upper respiratory tract infection, influenza, back pain, injection site reactions, myalgia
Comorbidities[30,31,36,37]	Proven safe to be used on patients with comorbid type 2 diabetes or stroke	Proven safe to be used on patients with comorbid type 2 diabetes

There is no data available for the usage of both drugs in pregnant women. Among the animal studies of alirocumab and evolocumab, it is found that alirocumab had no effect on embryo-fetal development in rats, but both drugs resulted in humoral immune suppression in infant monkeys when administered in the period from organogenesis through parturition.[5,20] Incidents of maternally-administered drug penetrating human placenta were reported in other monoclonal antibodies during the second and third trimester but not the first trimester.[5,20] Risk assessment should be done before prescribing alirocumab and evolocumab to pregnant women.

Comorbidities:

Concerning the prevalence of hyperlipidemia among diabetic patients, studies were conducted to prove the safety of both drugs on diabetic patients.[37] Supported by ODYSSEY DM-DYSLIPIDEMIA and DM-INSULIN clinical trial, alirocumab is effective in LDL-C reduction without compromising glycemic control in hyperlipidemic patients with comorbid type 2 diabetes.[36] For dyslipidemia patients comorbid with recent acute coronary syndrome, the safety of alirocumab was demonstrated in the ODYSSEY trial that the risk of stroke is reduced without increasing the risk of hemorrhagic stroke.[31]

INCLISIRAN

Proposed Indications

Inclisiran is a novel, synthetic small interfering RNA (siRNA) molecule designed to prevent PCSK9 synthesis in the liver **(Figure 1)**.[38] Developed by The Medicines Company, it is an investigational twice-yearly therapy currently in Phase III clinical development and its proposed indication is for the treatment of primary hypercholesterolemia in adults as adjunctive therapy to diet and in combination with other lipid-lowering therapies.[38] It is currently under review by FDA and European Medicines Agency for use in adults with ASCVD or HeFH who have elevated LDL-C while being on maximum tolerated dose of lipid-lowering therapy.[39] This siRNA therapeutic agent represents a new class of compounds that can reduce LDL-C.

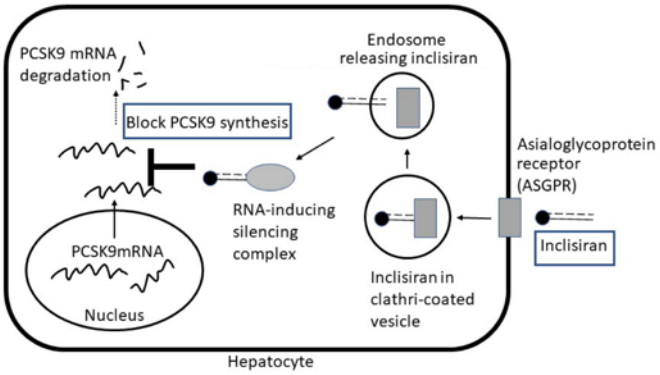

***Figure 1**: **The mechanism of PCSK9 synthesis inhibition by Inclisiran**. Inclisiran binds to ASGPR to cross the hepatocyte membrane. Endosome then releases inclisiran from the clathri-coated vesicle followed by formation of the RNA-inducing silencing complexes that cause PCSK9 mRNA degradation. As a result, PCSK9 synthesis is inhibited.*

Mechanism of action

siRNA are RNA molecules consisting of 20-30 molecules, which act as critical regulators in the expression and function of eukaryotic genomes.[40] Unlike long double-stranded RNA, siRNA molecules are able to escape from the mammalian interferon response and produce strong specific gene silencing.[40] They interfere with specific gene expression through varying the degradation of mRNA post transcription, thus avoiding translation of the complementary nucleotide sequences.[40]

Inclisiran, previously known as ALN-PCS, is a long-acting, synthetic siRNA directing against PCSK9.[40,41] It is made from one 2'-deoxy, eleven 2'-fluoro, and thirty-two 2'-Omethyl modified nucleotides, which are modified to the 3' end of the passenger strand with phosphorothioates.[41] The synthetic RNA molecule is then conjugated to triantennary N-acetylgalactosamine (GalNAc) carbohydrates, which is a ligand for abundant hepatocyte expressed asialoglycoprotein receptors (ASGPR).[40,41] This high-affinity binding of the GalNAc moiety with the ASGPR allows rapid uptake of inclisiran specifically into hepatocytes, thus requiring a lower dose of drug.[40,41]

Inside the hepatocytes, inclisiran binds to the RNA-induced silencing complex (RISC), enabling RISC to cleave the mRNA molecules that specifically encode PCSK9.[40,41] The cleaved mRNA is then degraded catalytically to prevent PCSK9 protein synthesis in the liver.[41] Therefore, one inclisiran-RISC complex could degrade several PCSK9 mRNAs.[41] Inhibition of PCSK9 synthesis then reduces the degradation of LDL receptors, prolonging their half-life to further uptake LDL from circulation.

Clinical Development of Inclisiran

Phase I study

In a randomized, placebo-controlled, phase I dose-escalation study including healthy volunteers with LDL-C ≥ 3.0 mmol/L, there was a significant reduction in circulating PCSK9 and LDL-C levels by 70% and 40% respectively, with high tolerability and safety up to the highest dose of 0.400 mg/kg inclisiran.[42] Moreover, the result also showed that not merely the extent but also the duration of reduction in PCSK9 and LDL-C were dose-dependent.[42]

In another randomized, placebo-controlled phase I clinical trial,[43] healthy volunteers with an LDL-C level of ≥ 2.6 mmol/L were investigated. Results illustrated that a single dose of ≥ 300 mg and 500 mg of inclisiran could reduce PCSK9 levels and LDL-C levels by up to 74.5% and 50.6%, respectively on day 84. Both reductions were sustained up till day 180.[43] For multiple-dose regimens, all decreased PCSK9 and LDL-C levels by up to 83.8% and 59.7% from baseline respectively on day 84. No serious adverse events with inclisiran were reported.[43] Overall, it is concluded that a dose of 300mg or more could reduce the level of PCSK9 and LDL-C for at least 6 months.[43]

ORION-7 is a phase I study specifically designed to assess the pharmacokinetics, pharmacodynamics, and safety of inclisiran in renally impaired patients.[44] For pharmacokinetics, $AUC_{0\text{-}inf}$ of inclisiran increased while its renal clearance reduced due to renal impairment.[44] However, the study reported that no difference in pharmacodynamic effects of inclisiran were observed between normal and renally impaired patients,[44] since dose greater than 300 mg would not cause any further LDL-C or PCSK9 reduction despite higher Cmax and AUC values.[43,44,45] The safety findings were also no notable difference across inclisiran-treated patients and placebo regardless of renal function. This may be a result of constant elimination of circulating inclisiran as the plasma concentrations were undetectable 48 hours post-dose in all groups of patients.[44] Hence, it is concluded that no renal dose adjustment is required for inclisiran.[44]

Phase II studies

ORION-1 was conducted to evaluate the efficacy, safety, and tolerability of inclisiran in patients with elevated LDL-C despite receiving a maximum possible dose of lipid-lowering therapy.[45] These subjects either have ASCVD with LDL-C levels ≥1.8mmol/L or non-ASCVD with LDL-C level ≥2.6mmol/L. Patients that had received two doses of 300 mg of inclisiran (on day 1 and day 90) manifested the greatest reductions of LDL-C and PCSK9, by up to 52.6% and 69.1% respectively on day 180.[45] Reduction after the first injection of inclisiran was first observed on day 14 and persisted until day 240, as illustrated by the mean reduction from baseline on day 240 in LDLC (47.2%) and for PCSK9 (56.1%).[45]

Considering safety, the percentage of adverse events reported to be the same among patients received inclisiran versus placebo. However, the

incidence of serious adverse events was higher in those who received inclisiran than placebo (11% and 8% respectively).[45] The most common adverse events included myalgia, headache, fatigue, nasopharyngitis, back pain, hypertension, diarrhea and dizziness.[45]

ORION-2 was a pilot study to investigate safety, tolerability, and efficacy of inclisiran in subjects with HoFH. Results demonstrated that the addition of inclisiran to statins and ezetimibe produced both LDL-C and PCSK9 reductions in 3 out of 4 HoFH patients.[46] Based on this finding, a larger Phase III study (ORION-5) on HoFH patients has been started.[38]

Phase III study

ORION-9,-10 and -11 are pivotal Phase III LDL-C lowering studies which were completed in the third quarter of 2019 and their articles were recently released in March 2020.[38] These trials investigated the efficacy, safety and tolerability of inclisiran treatment on LDL-C among different populations.[47,48] In these trials, participants received either 300mg inclisiran sodium or placebo by SC on day 1, day 90 and following every 6 months over a period of 540 days.[47,48]

ORION-9 focused on HeFH subjects whose LDL-C is at least 2.6 mmol/L despite receiving a maximum tolerated dose of statin therapy.[47] Results showed robust reductions in LDL-C levels of 39.7% in all genotypes of FH on day 540 after receiving subcutaneous injections of 300 mg of inclisiran on days 1, 90 270 and 450.[47] For safety, the overall percentage of adverse events was 76.8% in inclisiran group and 71.7% in placebo group. Although there were more injection-site adverse events in the inclisiran group (17% vs 1.7%), the reactions were generally mild and not severe or persistent.[47] The number of serious adverse events was relatively lower than that in the placebo group.[47]

Subjects with ASCVD were enrolled into ORION-10 whereas ORION-11 included subjects with or without ASCVD risks and had elevation of LDL-C despite receiving statin therapy at maximum tolerated dose.[48] ASCVD risk equivalent includes type 2 diabetes, familial hypercholesterolemia or a 10-year risk of a cardiovascular event of ≥20%.[48] After 2 doses of inclisiran on days 1 and 90, the overall LDL cholesterol levels were reduced by 52.3% in ORION-10, and by 49.9% in ORION-11 on day 510.[48] Similar incidence of adverse events was found in inclisiran-treated and placebo groups but more injection site reactions occurred in inclisiran-treated participants.[48]

Overall, Inclisiran can significantly lower levels of LDL-C, with an infrequent dosing regimen and an acceptable safety profile, in subjects with HeFH, ASCVD or ASCVD risk equivalents. The primary and secondary outcome in these 3 pivot trials were consistent with the results from Phase I and II studies.[43,45,47,48] These trials also demonstrated that inclisiran was well-tolerated without treatment-related hepatic or renal abnormalities.[47,48] Patients that have finished their Phase 3 studies are enrolling into ORION-8, an open-label and long-term extensive study evaluating the efficacy, safety and tolerability of inclisiran in long term dosing **(Table 2)**.

Convenient Storage

Inclisiran remains stable under a wide variety of thermal conditions. Therefore, refrigeration is not necessary for preservation, which makes transportation more convenient and inclisiran more suitable for use in the developing world.[49] In comparison, both alirocumab and evolocumab have to be stored in the refrigerator at 2°C to 8°C.[5,20] Alirocumab may be kept at room temperature up to 25°C for a maximum of 30 days in the original carton to protect from light, and storage above 25°C is prohibited.[5] It must be used within 30 days after removal from the refrigerator.[5] Evolocumab may be kept at 20°C to 25°C for 30 days, or else it should be discarded.[20] This suggests inclisiran to be a possible alternative when such storage condition or cold-chain distribution is not possible.[49]

CONCLUSION

Alirocumab and evolocumab are two registered PCSK9 inhibitors in Hong Kong. They are similar in terms of efficacy, target patient group and price. Alirocumab has more flexible dosing from 75mg-150mg every 2 weeks while evolocumab has a fixed dose of 140mg every 2 weeks. HeFH and HoFH are inherited genetic disorders that are caused by the autosomal dominant gene mutation, resulting in abnormally high LDL levels from birth.[50] Both drugs are approved to be used in HoFH and HeFH. HeFH refers to the inheritance of mutated FH gene from one affected parent whereas HoFH refers to the inheritance from both parents.[50] Given the rarity of HoFH patients, the sample size in clinical trials evaluating PCSK9 inhibitors in this population is relatively small.[51] Two and one small clinical trials have described the use of evolocumab and alirocumab respectively in patients with HoFH, which then supported the indication in HoFH.[51,52]

Inclisiran, a siRNA molecule, is a novel drug for treatment of hypercholesterolemia by preventing the synthesis of PCSK9 in the liver. Completed clinical trials reveal a comparable efficacy and safety profile of inclisiran to existing PCSK9 inhibitors, and its pharmacokinetic data reveals no hepatic or renal dose adjustment is needed. ORION-2 pilot study also suggests inclisiran may be a possible alternative PCSK9 targeting agent for treatment of HoFH. With the advantages of infrequent dosing and storage regimen, Inclisiran serves as a promising drug option in adults with ASCVD or HeFH who have elevated LDL-C while being on a maximum tolerated dose of lipid-lowering therapy. However, its long-term safety profile is yet to be established.

Table 2: Overview of clinical trials on Inclisiran

	Trials (Phase)	Relevant Endpoints	Patient Selected (numbers)	Results
Pivotal Trials	ORION-4 (III)[38]	CV outcome trial MACE endpoint	ASCVD (N=1500)	Estimated date of completion: December 2049
	ORION-5 (III)[38]	LDL-C primary endpoint	HoFH (N=59-60)	Estimated date of completion: June 2021
	ORION-9 (III)[47]	LDL-C primary endpoint	HeFH (N= 482)	An overall 39.7% LDL-C lowering Time-averaged placebo-adjusted reductions of 38.1% from days 90 through 540
	ORION-10 (III)[48]	LDL-C primary endpoint (US)	ASCVD (N=1561)	An overall 52.3% LDL-C lowering Time-averaged placebo-adjusted reduction of 53.8% from days 90 through 540
	ORION-11(III)[48]	LDL-C primary endpoint (EU)	ASCVD or ASCVD risk equivalent (N=1617)	An overall 49.9% LDL-C lowering Time-averaged placebo-adjusted reduction of 49.2% from days 90 through 540
Extension Trials	ORION-3 (II)[38] (extension of ORION-1 (II) with an active comparator (Evolocumab)	% change in LDL-C	ASCVD or ASCVD risk equivalent or HeFH (N=490)	Estimated date of completion: January 2022
	ORION-8 (III)[38] (extension of ORION-9, -10, -11)	LDL-C primary endpoint	ASCVD, ASCVD risk equivalent, HeFH (N=3,460)	Estimated date of completion: December 2023
Supportive Trials	Effect of an RNA interference drug on the synthesis of PCSK9 and the concentration of serum LDL-C in healthy volunteers: a randomised, single-blind, placebo-controlled, phase 1 trial (I)[42]	Safety, side effects & pharmacodynamics	Healthy subjects with LDL-C ≥ 3.0 mmol/L (N=32)	Safe & significant reduction in LDL-C
	A Highly Durable RNAi Therapeutic Inhibitor of PCSK9 (I)[43]	Safety, side effects & pharmacodynamics	Healthy subjects with LDL-C level of ≥ 2.6 mmol/L (N=69)	Safe & significant reduction in LDL-C
	ORION-1(II)[45]	% change in LDL-C	ASCVD or ASCVD risk equivalent or HeFH (N=501)	Up to - 35.5-52.6% at 180 days
	ORION-2 (II)[46]	% change in LDL-C	HoFH (N=4)	Up to ~43% at 180 days
Special Population Studies	ORION-6 (I)[38]	Pharmacokinetics, Pharmacodynamics, Safety	Hepatic impairment	Not Released
	ORION-7 (I)[44]	Pharmacokinetics, Pharmacodynamics, Safety	Renal impairment (N=31)	No renal dose adjustment is required
Others	ORION-12 (I)[38]	TQT (electrocardiographic effects)	Healthy subjects	Not Released

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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

Recent Development of Lipid Management: PCSK9 Inhibitors and Inclisiran

1. ***Which of the following statement is TRUE regarding Alirocumab and Evolocumab:***
   - A. Alirocumab is more effective than Evolocumab in ASCVD risk reduction
   - B. Evolucumab is more effective than Alirocumab as monotherapy for primary hyperlipidemia
   - C. Both drugs require dose adjustment for patient with moderate hepatic impairment
   - D. Dosage adjustment is not required in patients with mild or moderate renal impairment

2. ***Which of the following is the recommended dosing regimen for Alirocumab?***
   - A. Administered on day 1, day 90 and twice yearly thereafter
   - B. Administered every two weeks for one month and then every twelve weeks thereafter
   - C. Administered every 2 weeks or every 4 weeks
   - D. Administered on day 1 and once yearly thereafter

3. ***Which of the following is TRUE regarding clinical trials investigating the use of PCSK9 inhibitors in reducing cardiovascular risk?***
   - A. Efficacy of Alirocumab in preventing cardiovascular risk was slightly higher than Evolocumab when comparing results in ODYSSEY OUTCOMES and FOURIER
   - B. A consistent cardiovascular benefit on Evolocumab was found in patients with variable baseline LDL-C level in FOURIER
   - C. Results from ODYSSEY EAST showed a higher efficacy on Alirocumab in Asian population
   - D. In ODYSSEY LONG TERM, the rate of major adverse cardiovascular events was lower with Alirocumab than Ezetimibe

4. ***Which of the following statement is TRUE regarding PCSK9 inhibitors:***
   - A. PCSK9 inhibitors have been clinically proven can be safely used in pediatric patients and adolescents
   - B. The safety and efficacy of Evolocumab have been established in young patients with HoFH aged from 3 to 12
   - C. PCSK9 inhibitors are clinically proven to be used in patients with elevated LDL-C with or without history of ASCVD, HoFH and HeFHPCSK9 inhibitors are clinically proven can be safely used in diabetic patients
   - D. PCSK9 inhibitors are clinically proven can be safely used in pregnant women

5. ***Which of the following is FALSE regarding PCSK9 inhibitors?***
   - A. They are human monoclonal antibodies that bind to PCSK9 to prevent degradation of low-density lipoprotein receptors resulting in lowering LDL-C levels
   - B. Alirocumab does not have indication of treating homozygous familial hypercholesterolemia
   - C. No dosage adjustment is required when using it in patients with mild or moderate renal impairment
   - D. Some of the most common adverse reaction including nasopharyngitis, injection site reaction and influenza

6. ***Which of the following is FALSE regarding use of PCSK9 inhibitors and Inclisiran in homozygous familial hypercholesterolemia (HoFH)?***
   - A. HoFH patients require a larger reduction in LDL-C level, which can hardly be achieved with the use of statin and Ezetimibe only.
   - B. The efficacy of Evolocumab on HoFH was demonstrated by TESLA.
   - C. Inclisiran showed superior LDL-C level and apolipoprotein B reductions in ORION-2 when compared with Evolocumab.
   - D. Evolocumab and Inclisiran only have efficacy on HoFH patients with LDLR mutation on LDL receptors.

7. ***Which of the following clinical trials demonstrated efficacy and safety of using PCSK9 inhibitors on diabetic patients?***
   - (i) FOURIER
   - (ii) ORION-7
   - (iii) ODYSSEY DM-DYSLIPIDEMIA
   - A. (iii) only
   - B. (i) and (iii) only
   - C. (ii) and (iii) only
   - D. All of the above

8. ***Which of the following is the mechanism of action of Inclisiran:***
   - A. Interfering human DNA to prevent the PCSK9 synthesis in the liver
   - B. Interfering RNA molecule designed to prevent PCSK9 synthesis in the liver
   - C. Increase PCSK9 synthesis in the liver to reduce LDL-C
   - D. Increase the degradation of LDL receptors thus prolonging the time for LDL uptake from circulation

9. ***Which of the following is FALSE regarding mechanism of action of Inclisiran?***
   - A. It binds to RNA-induced silencing complex (RISC) and enable it to cleave the messenger RNA (mRNA) that encode PCSK9
   - B. With conjugation to triantennary N-acetylgalactosamine (GalNAc) carbohydrates, Inclisiran can target itself specifically to hepatocytes, hence reducing dose of drug
   - C. It is a long-acting synthetic small interfering RNA (siRNA) designed to reduce PCSK9 synthesis in liver
   - D. One Inclisiran-RISC complex could only degrade one PCSK9 mRNA

10. ***Which of the following is/are potential advantage(s) of using Inclisiran?***
    - (i) Less frequent dosing regimen
    - (ii) Both short-term and long-term safety are proven
    - (iii) Not requiring cold chain for storage
    - A. (ii) only
    - B. (i) and (ii) only
    - C. (i) and (iii) only
    - D. All of the above

Answers will be released in the next issue of HKPJ.

SHPHK – Thank you Hong Kong Pharmacists for Upholding their Professionalism to Provide Patient Service

Over the past few months, everyone has all been battling the 5th wave of COVID-19 in Hong Kong. The rapid spread of the Omicron coronavirus variant has led to overwhelmed healthcare systems. The Society of Hospital Pharmacists of Hong Kong (SHPHK) would like to express its sincere gratitude to all Pharmacists for their dedication to continuing to provide professional patient service to Hong Kong citizens during the epidemic.

Press Conference: Off-label Use of BioNTech COVID-19 Vaccine in Children

From left: Mr. Tony Lau, General Committee Member of SHPHK; Ms. Cherrie Li, Pharmacist of SHPHK; Mr. William Chui, President of SHPHK and; Ms. Michelle Zheng, Honorary Secretary of SHPHK.

A press conference was held by SHPHK on 23 January 2022. The aims of this press conference were to explain to the general public the difference between adult and paediatric BioNTech COVID-19 vaccine formulation and the feasibility of off-label use of BioNTech COVID-19 vaccine in children aged 5 to 11. After the press conference, we have received some very positive feedback from the general public via email!

The Society will continue to take every opportunity to promote health and drug safety on different occasions.

SHPHK Webinar: 5 to 11 age group specific COVID-19 Vaccination Clinical Lead Sharing

Children aged 5 to 11 may now start receiving fractional dose of BioNTech COVID-19 vaccine for adults at the Children Community Vaccination Centers (CCVCs). Since the amount of diluted vaccine required for children is very small, any air bubbles present in the syringe will severely affect the accuracy of the vaccine dose.

On 15 February 2022, SHPHK and the Hong Kong Society for Immunisations and Travel Medicine (HKSITM) organised a webinar to demonstrate how to optimise the safety and preparation of Paediatric BioNTech COVID-19 from adult formulation using both Low Dead-Volume (LDV) and non-LDV syringes. The Society would like to thank *Mr. Alex Leung, President of HKSITM* and *Mr. Michael Ling, Honorary Advisor of SHPHK* for sharing their experience regarding COVID-19 vaccine preparation with our Members.

SHPHK Webinar: Clinical Consideration of Using Oral Antiviral Therapy for Symptomatic Mild to Moderate COVID-19 Cases

Top left: Mr. Ng Man Keung, General Committee Member of SHPHK. Bottom, from left: Mr. Raymond Mak, Senior Pharmacist of Queen Mary Hospital; Mr. William Chui, President of SHPHK.

The two oral drugs for treating COVID-19, namely Nirmatrelvir / Ritonavir and Molnupiravir have recently arrived Hong Kong. A webinar regarding the two newly available COVID-19 antivirals was held on 2 April 2022. More than 140 pharmacists and pharmacy students were taking part in the webinar. The Society would like to thank *Mr. William Chui, President of SHPHK, Mr. Raymond Mak, Senior Pharmacist of Queen Mary Hospital* and *Mr. Ng Man Keung, General Committee Member of SHPHK* for taking time from their busy schedule to share with us the clinical considerations for the use of the two oral antivirals to treat COVID-19. Archive is now available on the SHPHK website (www.shphk.org.hk > Member Zone [Login required]).

Educational videos on COVID-19 vaccines

In February, the Society has produced three educational videos regarding COVID-19 vaccination in elderly, children and adolescents, and the efficacy of COVID-19 vaccines against SARS-CoV-2 variants. The three videos are now available on the Drug Education Resources Centre (DERC) website (www.derc.org.hk > 藥物視頻) as well as the SHPHK Youtube Channel (@香港醫院藥劑師學會).

Please feel free to recommend the videos to your colleagues, interns, students, patients, family members and friends!

Online Training: Reconstitution of BioNTech COVID-19 Vaccine - Preparation of Paediatric BioNTech Vaccine from Adult Formulation

In view of the rollout of BioNTech vaccine for children aged 5 to11 years in Hong Kong, the Department of Pharmacology and Pharmacy of the University of Hong Kong, the Hong Kong Academy of Nursing and SHPHK have jointly developed an online training programme which aims to provide further training to support the operational details on the preparation of paediatric BioNTech vaccine from adult formulation. Healthcare professionals involved in the central dilution process at the community vaccination centre can register for this training by scanning the QR code below:

You are most welcome to follow the Society's Facebook page (@SHPHK) and Instagram (@SHPHK1987) 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 pharmaceutical services in Hong Kong. Join us now as new member or renew your membership at the Society's website: www.shphk.org.hk.

2022 General Council of Pharmaceutical Society of Hong Kong and Pharmaceutical Society Charitable Foundation Limited

We are pleased to announce that the Annual General Meeting of The Pharmaceutical Society of Hong Kong (PSHK) and The Pharmaceutical Society Charitable Foundation Limited (PSCF) has been held at PSHK Clubhouse on 16th December 2021. The following members were elected for the tenure from 16th December, 2021 onwards for 2021-2022 term.

President:	Mr. Dick SUNG
Vice-presidents:	Ms. Beverley TAM Mr. Edward YAU
Hon. Secretary:	Mr. Jonathan NG
Hon. Treasurer:	Mr. Paul LAM
Council Members:	Mr. CHEUNG Wai Keung Mr. Ian CHEUNG Ms. CHEW Leng Leng Ms. Kathleen KUNG Mr. Vincent LAU Mr. Raymond LUK Mr. Rex NG Mr. Patrick TAM Ms. Sandra TSANG Mr. Edwin WONG
Pharmacy & Poisons Board Members:	Mr. Dick SUNG Ms. Beverley TAM Ms. Sandra TSANG

Advancing Hong Kong Pharmacy Profession Development – Local Continuing Education Programme

The Continuing Education (CE) programme launched in 2019, which is funded by the Professional Services Advancement Support Scheme, the Commerce and Economic Development Bureau, the Government of HKSAR.

This programme aims to upgrade local pharmacists with the latest professional knowledge and skills particularly on geriatric care, in order to meet the growing services demand for the ageing population in different settings. It consists of the one-day symposium and 12 training session of different topics, focusing on pharmacotherapy for elderly.

One-Day Symposium

The theme of the symposium was "Pharmaceutical Care for Healthy Ageing". It has been held successfully on 22 January 2022 in hybrid format. The symposium aims to facilitate the communication and experiences sharing between the international experts and the local pharmaceutical specialists.

We were honoured to have Professor Sophia Chan, Secretary for Food and Health to deliver an opening speech for the event. Six honorable speakers were from different regions including Hong Kong, Singapore, New Zealand and Taiwan. They presented and shared topics on geriatric care, community pharmacy practice and health informatics.

12 Training Sessions

As part of this CE programme, 12 training sessions have been arranged during June 2019 to March 2022. The sessions mainly focused on "elderly services/ diseases" which catered for the need in expanding pharmacist's roles in key advances in pharmaceutical care for the ageing population. The last training session was held on 29 March 2022, which also marked the end of this CE programme.

"Advancing Hong Kong Pharmacy Profession Development – Local Continuing Education Programme" was the very first structured CE programme organized by PSHK. We saw great turn out and feedback from our members and fellow pharmacists and would like to thank all of you for your support. A sincere appreciation to our collaborating organization the HKU LKS Faculty of Medicine Department of Pharmacy and Pharmacology.

PSHK will continue to serve the profession and better enable pharmacists by organizing more training courses in the future. Please stay tuned!

Prepared by Lucilla Leung

Active Ingredients:
Inclisiran

Pharmacological Properties:
Inclisiran is a cholesterol-lowering, double-stranded, small interfering ribonucleic acid (siRNA), conjugated on the sense strand with triantennary N-acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. In hepatocytes, inclisiran utilises the RNA interference mechanism and directs catalytic breakdown of mRNA for proprotein convertase subtilisin kexin type 9. This increases LDL-C receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation.

Indications:
Inclisiran is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with clinical atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH) who require additional lowering of LDL-C.

Contraindication:
Hypersensitivity to the active substance or to any of the excipients

Dosage Forms and Strengths:
Each pre-filled syringe contains inclisiran sodium equivalent to 284 mg inclisiran in 1.5 ml solution.

Each ml contains inclisiran sodium equivalent to 189 mg inclisiran.

Administration:
Method of administration: Subcutaneous use. Inclisiran is for subcutaneous injection into the abdomen; alternative injection sites include the upper arm or thigh. Injections should not be given into areas of active skin disease or injury such as sunburns, skin rashes, inflammation or skin infections.

The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months.

Interaction:
Inclisiran is not a substrate for common drug transporters and, although in vitro studies were not conducted, it is not anticipated to be a substrate for cytochrome P450. Inclisiran is not an inhibitor or inducer of cytochrome P450 enzymes or common drug transporters. Therefore, inclisiran is not expected to have clinically significant interactions with other medicinal products. Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

Dosage Available:
Leqvio solution for injection 284 mg/1.5 mL

Forensic Classification:
P1S1S3

Prepared by Ivy Chan

Active Ingredient:
Empagliflozin

Pharmacological Properties:
Empagliflozin is a reversible competitive inhibitor of SGLT2 with an IC50 of 1.3 nM. It has a 5000-fold selectivity over human SGLT1 (IC50 of 6278 nM), responsible for glucose absorption in the gut.

SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible as the predominant transporter for re-absorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes mellitus (T2DM) and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with T2DM by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent upon the blood glucose concentration and glomerular filtration rate (GFR). Through inhibition of SGLT2 in patients with T2DM and hyperglycaemia, excess glucose is excreted in the urine.

Indications:

Glycaemic control

Jardiance is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy

In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Reduction of risk of cardiovascular death

Jardiance is indicated in patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the risk of cardiovascular death.

Heart failure

Jardiance is indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients

Presentations:

One film-coated tablet contains empagliflozin 10 mg or 25 mg

Dose and Method of Administration:

Glycaemic control and Reduction of risk of cardiovascular death

The recommended starting dose of Jardiance is 10 mg once daily. In patients tolerating empagliflozin 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily. Jardiance can be taken with or without food.

Combination therapy

When Jardiance is used in combination with a sulfonylurea or with insulin, a lower dose of the sulfonylurea or insulin may be considered to reduce the risk of hypoglycaemia.

Heart failure

The recommend dose is 10 mg empagliflozin once daily.

Interactions:

Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension. Insulin and insulin secretagogues, such as sulfonylureas, may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with empagliflozin.

Forensic Classification:

P1S1S3

Errata for Volume 28(3) Sep-Dec 2021

In the article entitled “Survey of Physicians’ Perceptions on the Use of Oral Anticoagulants Among Patients With Atrial Fibrillation”, on page 83 & page 99, one of the names of the authors should be Wong, Ian CK instead of Wong, Lan CK.

Hong Kong Pharmaceutical Journal: For Detailed Instructions for Authors

INTRODUCTION

Hong Kong Pharmaceutical Journal (HKPJ) is the official publication of the Pharmaceutical Society of Hong Kong, the Practising Pharmacists Association of Hong Kong and the Society of Hospital Pharmacists of Hong Kong. It is a journal of the pharmacists, for the pharmacists and by the pharmacists. The Journal is currently divided into several sections: ***Editorial Comment; News & Short Communications; Pharmacy Practice; Over-the-Counter & Health; Drugs & Therapeutics; Primary Care; Herbal Medicines & Nutraceuticals; Pharmaceutical Technology*** and ***New Products***. It publishes review articles or original papers relevant to these different fields of pharmacy. In addition to the regular three issues of the Journal per year, there are issues dedicated solely to reports on special function of the society. The Aims and Scope of the Journal are published on the inside back cover of each issue.

Submission of Manuscript

Submission of a paper implies that it has not been published previously, that it is not under consideration for publication elsewhere, and that if accepted it will not be published elsewhere in the same form, in English or in any other language, without the written consent of the publisher. Authors are specifically discouraged from submitting papers as fragmented studies of a particular topic. A manuscript must be indicated which section it is belonged. Upon received, it will be screened by a Sectional Editor of HKPJ for initial consideration before it is sent out for further review or comment.

For submission:

Authors are encouraged to submit manuscripts to the editorial committee of HKPJ via editor@hkpj.org. In creating the electronic version of their manuscript, authors are requested to follow the guidelines for submitting files. The paper should be submitted as a single file, prepared with a standard word-processor such as Microsoft Word, with embedded tables and graphics. Please note that any embedded graphics must also be submitted as separate, original files. The preferred formats for graphics files are tiff or postscript. All correspondence between Editor and author is performed by email. Authors are reminded that the copyright of their article or paper is automatically transferred to HKPJ once it is accepted for publication in the journal.

Suggested Referees

Please submit, with your manuscript, the names and addresses of two potential referees. You may also mention persons who you would prefer not to review your paper.

Editorial Authority

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