

HONG KONG PHARMACEUTICAL *JOURNAL*

VOL 21 NO 4 Oct - Dec 2014 ISSN 1727-2874



News & Short Communications

Direct-to-consumer Advertising in Hong Kong – Possible Impact and Regulation

Treatment Updates on the Hepatitis C Infection (2 CE Units)

Rational Drug Design of Neuraminidase Inhibitors as Novel Anti-Influenza Agents

An Evidence-based Review on the Efficacy of Nutraceuticals for Migraine Prophylaxis in Adults

The Annual General Meeting and 65th Anniversary Dinner of the Pharmaceutical Society of Hong Kong

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

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

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

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We Need to Set Priorities Because There are More Battles Ahead



Welcome to read the last issue of volume 21 of the Hong Kong Pharmaceutical Journal!

Although we have just stepped into 2015 as this issue of the journal went to press, it is already getting close to celebrating the Chinese Lunar New Year. Hence, it is good for me to grasp this opportunity to wish you a prosperous year ahead full of joy, peace and happiness despite it is not

quite optimistic in real situation. Indeed, many people expect more battles ahead of us. But these battles unlike the one that was mentioned recently by a Government Officer from Mainland China; in which he meant more political restlessness ahead in Hong Kong while this editorial is talking about the eruption of some strange diseases in the region.

When we look back what had happened in the previous year, I believe no one would deny that last year was a horrifying year predominated by tragedies and strange diseases which have cost many people's life in most cases. Never before in human history, there were so many unusual crashes and shoot down of civilian aircrafts that took away many people's life simply because of some confrontations between different countries, races or mistakes in operation by human beings.

Besides the airplane crashes, news were almost subjugated by the epidemic of viral diseases. No matter in newspaper or on television, we were told about the number of casualty increase every day due to the spread of ebola virus. Starting from last March, news about the symptoms of this viral infection in West Africa countries had been reported. The viral epidemics, then spread swiftly from Africa to Europe and even as far as to North America. The outbreak of this viral disease has already led to the death of nearly nine thousand people despite intense international efforts to contain it.⁽¹⁾ The pandemic has caused panic among people as well as headaches for healthcare professionals and governments because there is no effective cure so far.

At about the same time, measles were found to resurge after three years of silence in some Beijing office buildings. At peak period, we were told that more than eleven thousands people were affected based on information disclosed by the Nation Health and Family Planning Commission of China.⁽²⁾ Although the outbreak was swiftly under control by demanding all people to take vaccination, the virus is not completely eliminated as infections continuous to be reported up to these days.

The problem of viral infection in Hong Kong is not better either in comparison to other parts of the world. More recently we heard about the outburst of a deadly flu which claims many deaths amongst the young and the old.⁽³⁾ The latest data indicates institutional outbreaks have seen no sign of decline for at least the next few months.

Being a pharmacist, we know that except for members of the Bedsonia virus which responds like rickettsias to broad-spectrum antibiotics, virus diseases are not susceptible to antibiotics or chemotherapeutic agents. Although in certain serious virus illnesses, particularly those liable to superinfection with bacterial pathogens, antibiotic treatment may be used to prevent complications, indiscriminate use of antibiotics in virus infections, such as measles may result in harm rather than benefit. However, what makes healthcare professionals worry most is that vaccination, which has been used for preventing the infection of viruses, may not work for some deadly viral diseases such as Sars, whooping cough, and more recently the ebola and flu. In a donor conference held in Berlin, Billionaire philanthropist Bill Gates warns people by saying that a more difficult pathogen [than Ebola] could come along a form of flu, a form of Sars or some type of virus that we haven't seen before. He commended that the risk of a worldwide pandemic meant it was reckless not to act now.

Before a global pandemic comes, it is important for us to put more effort into planning for future possible pandemic by building stronger health systems, improved surveillance and chains of supply and transportation, and fast-acting medical response teams like army. It is equally important for scientists and scholar to identify and design some novel drugs for curing the viral diseases as commended by Bill Gates.⁽⁴⁾ In this current issue, I have selected two remarkable review articles on antiviral diseases that I would like to highlight here. One is about the latest treatment strategies on patient infected with more resistant strain of Hepatitis C virion.⁽⁵⁾ In the other article, it talks about the design of a novel inhibitor for curing flu.⁽⁶⁾ It is not difficult to find out the authors of these two articles have adopted a rational approach based on unique targets and mechanistic action to discuss the anti-viral properties of some selected or novel designed drugs. With this approach, it could probably discover some more effective and specific therapeutics in the long run. I believe successful development of an effective drug against virus follow the tactic of know thyself and thy adversary.

I hope you enjoy reading them during the Chinese New Year holiday. And of course, don't forget to answer the questions prepared by the Pharmacy Central Continuing Education Committee for the purpose of your continuing education.

Cheung Hon-yeung
Editor-in-Chief
30th January, 2015.

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Prepared by Mr. Kwan Shek Him and Ms. Finna Kwok (Pharmacy Students of the Chinese University of Hong Kong)

Australia: Safety Advisory - Potential Confusion in Reading Correct Dose of Children's Panadol 1-5 Years Colourfree Suspension

Date: October 14, 2014

The Therapeutic Goods and Administration (TGA) has become aware that some people have expressed confusion over how to use measuring syringes supplied with Children's Panadol 1-5 Years Colourfree Suspension. Incorrect measurements have the potential to lead to accidental overdoses.

The syringe supplied with Children's Panadol 1-5 Years Colourfree Suspension is shaped in such a way that the dose should be measured where the widest side of the plunger meets the barrel of the syringe. This differs from most syringes which measure to the tip of the plunger where the liquid finishes. With the Children's Panadol syringe, the liquid continues past the tip of the plunger and therefore needs to be measured to where the widest sides of the plunger meet the barrel of the syringe. If the dose is measured from the point where the liquid touches the end of the plunger closest to the nozzle, the dose is incorrect, resulting in undesirable effects.

The TGA is working with GSK to address any potential for accidental overdose, including whether an update to the packaging of Children's Panadol 1-5 Years Colourfree Suspension to clarify the instructions on how to use the dosing syringe is sufficient or if other actions are also required.

In Hong Kong, a series of Panadol products are registered by GlaxoSmithKline (GSK). Amongst them, there are seven registered pharmaceutical products containing paracetamol in liquid dose form. According to GSK, Panadol Suspension 120mg/5ml (HK-52694) is the only product currently marketed in Hong Kong and it contains a measuring cup for dose measurement instead of a syringe. GSK agreed to inform the Department of Health regarding the arrangement of the syringe shall other products that are not marketed be re-introduced into Hong Kong.

Source: www.drugoffice.gov.hk

The United Kingdom: MHRA Statement on Misuse of Laxatives

Date: October 18, 2014

Following the BBC Watchdog investigation into the availability of stimulant laxatives in the UK, first broadcast on Thursday 16 October, an MHRA spokesperson made a statement.

Most laxative medicines are used by patients safely and in accordance with the instructions for use on the patient information leaflet (PIL). The Patient and Public Engagement Expert Advisory Group (EAG) which reports to the Commission on Human Medicines (CHM) has recently reviewed the patient information for non-prescription laxatives and has recommended that stronger warnings should be added emphasising that taking laxatives regularly for a long time is harmful and they do not aid weight loss. MHRA is currently working with companies of stimulant laxative products to

introduce these updated warnings which should provide consistency across the range of stimulant laxative products available.

In Hong Kong, there are 112 registered pharmaceutical products containing stimulant laxatives, including bisacodyl, docusate sodium, glycerol, senna (e.g. sennoside, senna leaf powder, etc.), casanthranol and sodium picosulfate. In view of the above announcement, the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board. The DH would keep vigilant on the updates of the announcement by the health authority.

Source: www.drugoffice.gov.hk

Canada: Health Canada Reviewing Possible Safety Concerns with Certain Long-term Antiplatelet (Blood Thinner) Therapy; Benefits of Treatment still Outweigh Potential Risks

Date: November 19, 2014

Health Canada is aware of and will be reviewing new evidence on the safety of long-term use of the prescription blood-thinners clopidogrel (Plavix) and prasugrel (Effient). Clopidogrel and prasugrel reduce the risk of blood clots in patients who have had a heart attack, stroke or related blood clotting diseases.

Health Canada has not reached new conclusions or made recommendations regarding clopidogrel or prasugrel safety at this time. The benefits of clopidogrel and prasugrel in protecting against blood clots continue to outweigh their risks when used as directed.

The new evidence is from the Dual Antiplatelet Therapy (DAPT) Study, a large-scale, multi-national clinical trial that evaluated 12

versus 30 months of clopidogrel or prasugrel use with ASA, known as dual antiplatelet therapy. Published in the New England Journal of Medicine, the study looked at how these drugs can prevent blood clots in patients with coronary stents. Currently, Health Canada is evaluating preliminary information from the study, which found that 30 months of dual antiplatelet therapy was beneficial in reducing blood clots and heart attacks relative to 12 months, but saw an increase in deaths due to non-cardiovascular causes in the 30-month group versus the 12-month group.

Source: www.drugoffice.gov.hk

Canada: New Dosage Recommendations for IMOVANE® (Zopiclone) to Minimize the Risk of Next-day Impairment

Date: November 20, 2014

Sanofi-aventis Canada Inc., in collaboration with Health Canada, informed healthcare professionals and the public about important new dosing information which has been added to the local Product Monograph for IMOVANE (zopiclone) related to the risk of next-day impairment. Even if IMOVANE is taken as instructed, some patients may still have zopiclone blood levels high enough to produce impairment.

The recommended starting dose has been reduced to 3.75 mg (one-half of the 7.5 mg tablet). IMOVANE should be taken once per night at bedtime. The lowest effective dose for each patient should be used. The prescribed dose should not exceed 5 mg in elderly patients, in patients with hepatic or renal impairment or those currently treated with potent CYP3A4 inhibitors. Dose adjustment

may be required with concomitant use with other CNS-depressant drugs. Treatment with IMOVANE should usually not exceed 7-10 consecutive days. Use for more than 2-3 consecutive weeks requires complete re-evaluation of the patient.

Patients should be instructed to wait for at least 12 hours after dosing before any other activities requiring full mental alertness, especially for elderly patients and for patients who take the 7.5 mg dose. Patients should be advised on the risk of next-day impairment and that this risk is increased if dosing instructions are not carefully followed, and that impairment can be present despite feeling fully awake.

Source: www.drugoffice.gov.hk

European Union: No Consistent Evidence of an Increased Risk of Heart Problems with Testosterone Medicines

Date: November 22, 2014

The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) of European Medicines Agency (EMA), a regulatory body representing EU Member States, has agreed by consensus that there is no consistent evidence of an increased risk of heart problems with testosterone medicines in men who lack the hormone (a condition known as hypogonadism). However, the lack of testosterone should be confirmed by signs and symptoms and laboratory tests before treating men with these medicines.

The PRAC recommended updating the product information in line with the latest evidence and to provide warnings about those who might be at increased risk of heart problems. The product information should make it clear that testosterone should only be used when an abnormally low level of the hormone has been confirmed by signs and symptoms and appropriate laboratory tests. It should be

noted that although testosterone levels naturally fall somewhat with age, but restoration of these levels in healthy older men is not an authorised use of the medicine in the EU.

In Hong Kong, there are eight registered pharmaceutical products containing testosterone and they are prescription-only medicines. Letters to inform local healthcare professionals on the above safety warnings and the latest EU PRAC recommendations were issued on 20 June 2014, 16 July 2014 and 13 October 2014. So far, DH has not received any adverse drug reaction report on the drug related to cardiovascular complications. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board, and will continue to keep vigilant on further announcements on the products issued by other overseas health authorities.

Source: www.drugoffice.gov.hk

European Union: CMDh Agrees to Strengthen Warnings on the Use of Valproate Medicines in Women and Girls

Date: November 22, 2014

The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) a regulatory body representing EU Member States, has agreed to place stronger emphasis on the risks in women and girls. Valproate should be taken only when clearly necessary, due to malformations and developmental problems caused by fetal exposure to valproate.

Doctors in the EU are now advised not to prescribe valproate for epilepsy or bipolar disorder in pregnant women, in women who can become pregnant or in girls unless other treatments are ineffective or not tolerated. Those for whom valproate is the only option for epilepsy or bipolar disorder should be advised on the use of effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions. However, women

and girls should not stop taking the prescribed valproate without consulting their doctor.

In Hong Kong, there are 10 registered pharmaceutical products containing valproate/valproic acid and they are prescription-only medicines. The Registration Committee of the Pharmacy and Poisons Board (the Registration Committee) had decided that the package inserts or sales packs of the affected products should be updated to include the new safety warnings. Letter to inform local healthcare professionals on the latest EMA and MHRA recommendations of the products was issued on 13 October 2014. So far, the Department of Health (DH) has not received any adverse drug reaction in connection to the drug.

Source: www.drugoffice.gov.hk

European Union: Investigation into Reports of Serious Adverse Events Following Use of Fluad

Date: November 29, 2014

The European Medicines Agency (EMA) is working with the Italian medicines agency (AIFA) and other EU medicines regulatory authorities to investigate the cause of serious adverse events, including deaths, in a small number of elderly patients who had received Fluad flu vaccine. There is so far no evidence to suggest a causal link between the vaccine and the reported adverse events. The suspension is a precautionary measure.

AIFA has suspended the use of two batches of the flu vaccine produced by Novartis. Testing of the batches is underway, as well as a detailed analysis of the case reports from Italy. This includes examining all available information on the affected patients' age, health condition and medication regime.

In Hong Kong, Fluad Vaccine Pre-filled Syr Inj (HK-50982) is registered by Novartis Pharmaceuticals (HK) Ltd. (Novartis), and is a prescription-only medicine. According to Novartis, the affected two batches of Fluad vaccine suspended by the Italy health authority have not been imported into HK. As a precautionary measure, Novartis has decided to hold all distribution of Fluad vaccine in HK, and will follow-up for the latest situation on the incident in Italy. The Department of Health (DH) has not received any local adverse drug reaction reports related to Fluad vaccine. DH will follow-up with Novartis for the latest situation on the incident in Italy, and will remain vigilant on future announcements related to Fluad vaccine by the EU and other overseas health authorities. DH will also keep local healthcare professionals posted when there are new findings on the incident.

Source: www.drugoffice.gov.hk

Canada: Health Products Quarantined from two Sites in India as Health Canada Assesses Data Integrity Concerns

Date: December 24, 2014

At Health Canada's request, Canadian importers have agreed to quarantine health products from the Dr. Reddy's Laboratories in Srikakulam and the IPCA Laboratories in Pithampur due to data integrity concerns. This action comes in light of recent information from a trusted regulatory partner that raises concerns about the reliability of the laboratory data generated at these sites. Health Canada is taking this action as an interim precautionary measure to help mitigate any potential risk. A quarantine means that the Canadian importers have agreed to stop the importation and distribution of products from these two sites. At this time there is no identified risk to health, and Health Canada is not requesting a recall of any of the products.

Health Canada's action applies to active pharmaceutical ingredients (APIs) from Dr. Reddy's Laboratories as well as to finished drug products from a different IPCA Laboratories facility than is currently subject to import restrictions by Health Canada. To

date, none of the affected products have been determined by Health Canada to be medically necessary.

In Hong Kong, seven registered pharmaceutical products are involved in the incident, namely Capecitabine Sandoz Tablet 150mg (HK-62913) and Capecitabine Sandoz Tablet 500mg (HK-62914) which are registered by Novartis Pharmaceuticals (HK) Ltd. (Novartis), and PMS-Valsartan Tablets 40mg (HK-62346), 80mg (HK-62378), 160mg (HK-62377), 320mg (HK-62376) and PMS-Domperidone Tab 10mg (HK-47297) which are registered by Trenton-Boma Ltd. (T-Boma). All of the products are prescription-only medicines except PMS-Domperidone Tab 10mg which is a pharmacy-only medicine. Both Novartis and T-Boma confirmed that the above mentioned products are not manufactured with Active Pharmaceutical Ingredient (API) from the affected sites. The Department of Health will keep vigilant on the updates from Health Canada for consideration of any actions deemed necessary.

Source: www.drugoffice.gov.hk

Singapore: Risk of Cardiovascular, Neurological and Psychiatric Adverse Effects Associated with Bromocriptine

Date: December 27, 2014

Health Sciences Authority (HSA) would like to remind healthcare professionals about the risk of cardiovascular, neurological and psychiatric adverse effects that are known to be associated with the use of bromocriptine. Bromocriptine is a dopamine agonist that has been authorized across Europe for use in the prevention and suppression of lactation postpartum.

The review done by PRAC in 2014 concluded that although bromocriptine was effective for the prevention or suppression of lactation postpartum, an association between bromocriptine treatment and adverse events such as heart attack, stroke, fits, and psychiatric disorders could not be ruled out. PRAC recommended that bromocriptine should only be used in the presence of compelling medical reasons for stopping lactation. Bromocriptine should not be used routinely for prevention or suppression of lactation, nor to relieve

symptoms of pain or swelling of the breasts postpartum. In addition, women at high risk of serious adverse effects, such as those with severe psychiatric disorders and those with disorders that increase blood pressure, should not be treated with bromocriptine. Blood pressure monitoring is recommended in patients using bromocriptine to detect early signs of problems.

Healthcare professionals are advised to take into consideration the labelled warnings regarding cardiovascular, neurological and psychiatric concerns when prescribing bromocriptine to patients. They should also be aware of the above safety review by PRAC and its recommendations on the use of bromocriptine for suppression of lactation as authorized in Europe.

Source: <http://www.hsa.gov.sg>

Singapore: Risk of Hypoglycaemia Associated with Hydroxychloroquine or Chloroquine

Date: December 27, 2014

Health Sciences Authority (HSA) would like to inform healthcare professionals about the risk of hypoglycaemia associated with the use of hydroxychloroquine or chloroquine. Hydroxychloroquine and chloroquine are anti-malarial drugs. Hydroxychloroquine is also indicated for the treatment of rheumatoid arthritis, juvenile chronic arthritis, discoid and systemic lupus erythematosus and dermatological conditions caused or aggravated by sunlight.

Hydroxychloroquine is known to potentiate the hypoglycaemic effects of anti-diabetic agents. However, the risk of hypoglycaemia with hydroxychloroquine was also observed in patients who were not on concomitant hypoglycaemic agents. Besides, the authors of a published overseas case report postulated that the hypoglycaemia was associated with chloroquine poisoning. Moreover, in vitro evidence has shown that chloroquine reduces intracellular insulin degradation, increases intracellular insulin accumulation, slows receptor recycling and stimulates insulin-mediated glucose transport. In animal studies, chronic chloroquine treatment was found to enhance insulin release in rats while treatment of diabetic rats with hydroxychloroquine led to higher insulin levels and lower glucose concentrations.

The European Medicines Agency recommended that the product labelling for hydroxychloroquine and chloroquine should be strengthened on the risk of hypoglycaemia associated with their use. Health Canada has also concluded from its assessment that there is sufficient evidence to support a causal association between hydroxychloroquine use and the onset of hypoglycaemia, including serious cases involving a loss of consciousness and hospitalisation. Healthcare professionals are advised to be vigilant to possible signs and symptoms of hypoglycaemia in patients prescribed hydroxychloroquine or chloroquine, regardless of concomitant use of hypoglycaemic agents.

In Hong Kong, there are three registered pharmaceutical products containing hydroxychloroquine and one containing chloroquine. All of them are prescription-only medicines. So far, DH has not received any adverse drug reaction report on the drugs related to hypoglycaemia. A letter to healthcare professionals to draw their attention on the new safety findings will be issued, and the matter will be discussed in the meeting of the Registration Committee of the Pharmacy and Poisons Board.

Source: www.drugoffice.gov.hk

Singapore: Risk of Thrombotic Microangiopathy and Nephrotic Syndrome Associated with the Use of Interferon Beta Products

Date: December 27, 2014

Health Sciences Authority (HSA) would like to update healthcare professionals on overseas cases of thrombotic microangiopathy (TMA) and nephrotic syndrome that have been reported with the use of interferon beta products. Interferon beta products is approved for the treatment of relapsing multiple sclerosis and treatment of patients with a single demyelinating event with an active inflammatory process, who are determined to be at high risk of developing relapsing multiple sclerosis. It is also approved for the treatment of secondary progressive multiple sclerosis with active disease.

Overseas post-marketing cases of TMA, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with the use of interferon beta products. A total of 13 reports of TMA, TTP and/or HUS that occurred with interferon beta were received by the UK Medicines and Healthcare Products Regulatory Agency. Clinical

features of TMA include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g., confusion and paresis) and impaired renal function. Overseas cases of nephrotic syndrome with different underlying nephropathies have also been reported in patients treated with interferon beta. Early signs and symptoms of nephrotic syndrome include oedema, proteinuria and impaired renal function, especially in patients at high risk of renal disease. Both TMA and nephrotic syndrome may develop several weeks to several years after starting treatment with interferon beta.

Healthcare professionals are advised to monitor and consider the possibility of TMA and nephrotic syndrome in patients treated with interferon beta products, if signs and symptoms consistent with these diagnoses are identified.

Source: <http://www.hsa.gov.sg>

Singapore: Update on Trend of Lymphadenitis and Injection-site Reactions with The BCG Vaccine SSI

Date: December 27, 2014

In Singapore, the Bacillus Calmette-Guerin (BCG) vaccine SSI® is routinely administered to all neonates at birth as part of the National Childhood Immunisation Schedule (NCIS). As of end August 2014, the estimated incidences of suppurative lymphadenitis and non-suppurative lymphadenitis for the 2009 to 2013 vaccinated cohorts ranged from 0.48 to 3.18 per 1,000 vaccinees and 0.10 to 0.79 per 1,000 vaccinees, respectively. Following a peak in cases reported in the 2011 vaccinated cohort, the incidences of suppurative and non-suppurative lymphadenitis have since returned to baseline levels.

Health Sciences Authority's (HSA) investigation revealed that the higher incidence of suppurative lymphadenitis involving the 2011 vaccinated cohort may be batch-related as a result of vaccine manufacturing issues. Further investigation conducted by the manufacturer identified the possible cause to be due to a period of manufacturing with a slower growth of the bacilli. One postulation could be that the higher level of bacterial by-products as a result of the slower growth of the bacilli may have triggered

lymphadenitis in some patients. The trending of the incidence of suppurative lymphadenitis of all batches administered from 2009 to 2013 in Singapore appeared to be consistent with the manufacturer's investigation.

HSA also wishes to highlight to healthcare professionals that neonates who were administered the BCG vaccine at the gluteal area appeared to have experienced more injection-site reactions compared to those who were vaccinated at the deltoid area. A total of 13 cases (0.14 per 1,000 vaccinees) of abscess or cellulitis were reported in children who were vaccinated at the gluteal area compared to six cases (0.10 per 1,000 vaccinees) in those vaccinated at the deltoid area for the 2010 to 2013 vaccinated cohorts. This may be contributed in part by the difficulty in caring for the injection site when the vaccine was administered at the gluteal area. Healthcare professionals are advised to take this into consideration during the administration of the BCG vaccine.

Source: <http://www.hsa.gov.sg>



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- GENTLE FINE MIST improves patient experience compared to a conventional nasal spray⁵:
- No smell, with less aftertaste, less drip down the nose or throat
- Indicated for patients as young as 2 years old⁶



Integrated Safety Information: CONTRAINDICATIONS: Avamys Nasal Spray is contra-indicated in patients with hypersensitivity to any of the ingredients. **WARNINGS AND PRECAUTIONS:** - undergoes extensive first-pass metabolism by the liver enzyme CYP3A4, therefore the pharmacokinetics of intranasal fluticasone furoate in patients with severe liver disease may be altered. Based on data with another glucocorticoid metabolised by CYP3A4, co-administration with ritonavir is not recommended because of the potential risk of increased systemic exposure to fluticasone furoate. Systemic effects with nasal corticosteroids have been reported, particularly at high doses prescribed for prolonged periods. The following adverse events have been reported with a frequency of $\geq 1/100$ to $1/10$ (common) and $\geq 1/10$ (very common) **CLINICAL TRIALS DATA:** Very common: Epistaxis; Common: Nasal ulceration **POST-MARKETING DATA:** Common: Headache Please refer to the full prescribing information for further information and prior to administration.

AVAMYS™ NASAL SPRAY Abbreviated Prescribing Information: INDICATIONS AVAMYS is indicated for the treatment of the symptoms of seasonal and perennial allergic rhinitis in patients 2 years of age and older. **DOSAGE AND ADMINISTRATION** Administer AVAMYS (27.5mcg/spray) by the intranasal route only. Adults & adolescents ≥ 12 years: The recommended starting dosage is 110mcg (2 sprays in each nostril) once daily. When the symptoms have been controlled, reducing the dosage to 55mcg (1 spray in each nostril) once daily may be effective for maintenance. Children 2-11 years: The recommended starting dosage in children is 55mcg (1 spray in each nostril) once daily. Children not adequately responding to 55mcg may use 110mcg (2 sprays in each nostril) once daily. Once symptoms have been controlled, the dosage may be decreased to 55mcg once daily. **CONTRAINDICATIONS** Hypersensitivity to any of the ingredients. **WARNINGS AND PRECAUTIONS** AVAMYS undergoes extensive first-pass metabolism by CYP3A4, therefore the pharmacokinetics of AVAMYS in patients with severe liver disease may be altered. Co-administration with ritonavir is not recommended. **INTERACTIONS** In a drug interaction study of AVAMYS with the potent CYP3A4 inhibitor ketoconazole there were more subjects with measurable AVAMYS plasma concentrations in the ketoconazole group compared to placebo. The enzyme induction and inhibition data suggest that there is no theoretical basis for anticipating metabolic interactions between AVAMYS and the cytochrome P450-mediated metabolism of other compounds at clinically relevant intranasal doses. Therefore, no clinical studies have been conducted to investigate interactions of AVAMYS on other drugs. **PREGNANCY AND LACTATION** Adequate data are not available regarding the use of AVAMYS during pregnancy and lactation in humans. AVAMYS should be used in pregnancy only if the benefits to the mother outweigh the potential risks to the foetus. Following intranasal administration of AVAMYS at the maximum recommended human dose (110mcg/day), plasma AVAMYS concentrations were typically non-quantifiable and therefore potential for reproductive toxicity is expected to be very low. **ADVERSE REACTIONS** Epistaxis, nasal ulcerations. Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria. Headache, Rhinalgia, nasal discomfort (including nasal burning, nasal irritation and nasal soreness), nasal dryness. **OVERDOSE** Acute overdose is unlikely to require any therapy other than observation. Abridged PI (GUS 07/PI06)

Please refer to the full prescribing information before prescribing. Full prescribing information is available upon request.

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For adverse events reporting, please call GlaxoSmithKline Limited at (852) 9046 2498.
The material is for the reference and used by healthcare professionals

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Direct-to-consumer Advertising in Hong Kong – Possible Impact and Regulation

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ABSTRACT

In recent years, the general public is more involved in the management of its own health and has become a target for medicine promotion by means such as direct-to-consumer advertising (DTCA) of prescription drugs. Although DTCA is banned in most countries of the world, Hong Kong does not have an entire ban. This paper will discuss the impacts of DTCA from the experience of foreign countries and limited data in Hong Kong and the possible regulatory options that can be adopted by Hong Kong.

Keywords: Health management, direct-to-consumer advertising, prescription drug advertising, impact, regulation

INTRODUCTION

In the past, prescription drugs were only promoted to healthcare professionals, but during the early 1990s, the Food and Drug Administration (FDA) of the United States observed that some manufacturers promoted these drugs to patients directly and this had been termed direct-to-consumer advertising (DTCA).⁽¹⁾ DTCA has remained controversial for a long period of time, especially after the regulation of DTCA was relaxed by the FDA in 1997.⁽²⁾ Till now, DTCA is allowed in the United States and in New Zealand.⁽³⁾ It is suggested that DTCA can promote the use of medicines in previously untreated disease but it can also lead to overuse of medicines.⁽⁴⁾

In many countries, drug advertisement for prescription drug is regulated differently from over-the-counter (OTC) drugs. For example, in the United States, the FDA regulates the advertisements for prescription drugs and the Federal Trade Commission regulates those for OTC drugs.⁽⁵⁾ In the United Kingdom, only medicines classified as Pharmacy Sale or General Sale List can be advertised to the public while the advertising of a prescription only medicine to the public is prohibited.⁽⁶⁾ In Hong Kong, pharmaceutical advertising is regulated by the Undesirable Medical Advertisements Ordinance (UMAO). However, the ordinance mainly regulates pharmaceutical advertising based on the indications of medications and it does not directly regulate the DTCA. For example, the UMAO prohibits advertising of drugs for any respiratory diseases, such as asthma, but exempt the advertising of drugs for the relief of hay fever symptoms.⁽⁷⁾ Therefore, an OTC drug is prohibited from advertising its use for asthma but a prescription drug is allowed to make

advertisement for relieving symptoms of hay fever. To conclude, DTCA is only partially prohibited in Hong Kong.

If there is no appropriate regulation on DTCA, it may grow rapidly in Hong Kong and may affect the health of the public. This paper will provide some possible risks and benefits of DTCA from a prolific literature review and discuss the regulations on DTCA in other countries to provide ideas on how DTCA can be regulated in Hong Kong.

HISTORY OF DTCA IN THE UNITED STATES

The history of DTCA was greatly affected by the related regulations in US, which has abundant DTCA and detailed guidelines on DTCA. Also, most of the literature is based on US. Therefore, its history will be introduced with the development of DTCA.

The FDA had no authority over advertising of both OTC and prescription drugs until the US Congress passed the Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act (FDCA) in 1962, which required prove of safety and effectiveness of drugs before marketing.⁽⁸⁾ In 1969, the FDA released its advertising regulations which required prescription drug advertisements to give a fair balance between information about the side effects and contraindications of the drug and information about the effectiveness of the drug.⁽⁸⁾ The regulations are indirectly related to DTCA in two ways. First, it required advertisement to public through broadcasting media including radio, television, or telephone, to contain a brief summary of all necessary information related to side effects and contraindications unless an adequate provision is made. Second, it exempted reminder advertisements and help-seeking advertisements which mentioned only the name of the drug or a disease respectively.⁽⁸⁾

Before 1980s, drug companies gave information of prescription drugs only to doctors and pharmacists⁽⁹⁾ so there were no special concerns on the effects of these advertisements on the public. However, during 1980's, drug companies started DTCA to give the public more direct access to information of prescription drugs.⁽⁹⁾ One such initial example was the print and television advertisements of a prescription pain reliever, Rufen, launched by Boots pharmaceuticals.⁽⁸⁾ Since then, pharmaceutical industry increased the amount and spending of DTCA. From 1991 to 1995, the industry spending on DTCA increased from \$55 million to \$363 million.⁽⁸⁾ The

pharmaceutical industry also sought the definition of adequate provision which can replace the brief summary in broadcast advertisements and the FDA faced an increased pressure to ease the regulations.⁽⁸⁾ In 1997 and 1999, the FDA clarified the definitions of adequate provision as mentioned before to explain how pharmaceutical industry could meet the requirements of broadcasting advertisements.^(10,11) In 2004, the FDA further loosened its regulation so that a complete prescribing information in print product claim advertisements could be replaced by the inclusion of a “simplified brief summary”. This allowed information to be presented with only the major risks and in simplified language.⁽¹²⁾

REGULATIONS ON PHARMACEUTICAL ADVERTISING IN HONG KONG

The publication of advertisements for medicine, surgical appliance or treatment in Hong Kong is restricted by the Undesirable Medical Advertisements Ordinance (UMAO) which was first enacted in 1953.⁽¹³⁾ The UMAO prohibits the publication of advertisements that are related to treating or preventing contraction of any specified disease or condition, including:⁽⁷⁾ (1) benign or malignant tumour, (2) viral, bacterial, fungal or other infectious disease, (3) parasitic disease, (4) venereal disease, (5) respiratory disease, (6) disease of the heart or cardiovascular system, (7) gastro-intestinal disease, (8) disease of the nervous system, (9) disease of the genitourinary system, (10) disease of the blood or lymphatic system, (11) disease of the musculo-skeletal system, (12) endocrine disease, (13) organic condition affecting sight, hearing or balance and (14) disease of the skin, hair or scalp except specified purposes that are exempted, such as relief of symptoms of aphthous ulcer, symptomatic relief of headaches, and prevention of pimples.⁽⁷⁾

In addition, the advertisements related to abortion or treating human for: (1) induction of menstruation or relief of amenorrhea or delayed menstruation or any other gynaecological or obstetrical disease, (2) promotion of sexual virility, desire or fertility, or the restoration of lost youth and (3) correction of deformity or the surgical alteration of a person's appearance are also prohibited.⁽⁷⁾

In 2005, the Undesirable Medical Advertisements (Amendment) Ordinance (UMA(A)O) was enacted to prohibit or restrict advertising to six groups of specified claims of orally consumed products.⁽¹³⁾ The prohibited claims include:⁽⁷⁾ (1) prevention, elimination or treatment of breast lumps, (2) regulation of the function of the genitourinary system and/ or improvement of symptoms of genitourinary problems and (3) regulation of the endocrine system and/ or maintenance or alteration of hormonal secretions.

Three claims were also restricted with prescribed permissible claims, including:⁽⁷⁾ (1) regulation of body sugar or glucose and/or alteration of the function of the pancreas, (2) regulation of blood pressure and (3) regulation of blood lipids or cholesterol.

In addition, television and sound broadcasting advertisements are further regulated by the Broadcasting Ordinance (Chapter.562) and the Broadcasting (Miscellaneous Provisions) Ordinance (Chapter.391). These two ordinances allowed the establishment of Code of Practice by the

Communications Authority, a Hong Kong statutory body, to provide practical guidance to the broadcasting industry.^(14,15) Advertising in television and radio program are regulated by the Generic Code of Practice on Television Advertising Standards and Radio Code of Practice on Advertising Standards respectively. These two Codes of Practice specified that drugs included in Part I of the Schedule to the Poisons List Regulations or Schedule 1 to the Antibiotics Regulations in television and radio programs are not allowed.^(16,17) Since prescription drugs in Hong Kong belongs to the Third Schedule poisons of Part I of the Poisons List⁽¹⁸⁾ or Schedule 1 of the Antibiotics Regulations,⁽¹⁹⁾ their advertising is not allowed on television or radio.

Apart from law regulation, the Hong Kong Association of the Pharmaceutical Industry (HKAPI) has published the Code of Pharmaceutical Marketing Practices that regulates drug advertising by its members. In earlier editions, this code of practice stated that ‘Medicines must not be advertised to the general public if they are prescription-only medicines.’, but in later version since 2000, this restriction had been changed to ‘Information about medicines which is made available to the general public either directly or indirectly must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product’,^(20,21) which endorsed DTCA with some restrictions.

Therefore, DTCA is not banned entirely in Hong Kong and prescription drug advertising can be published if it does not violate the regulations.

DTCA IN HONG KONG

Because of the relaxation of the Code of Pharmaceutical Marketing Practices, DTCA of some ‘lifestyle’ drugs for treatment of obesity and hair loss started to appear in Hong Kong on newspapers and magazines since 2000 and the expenditure on DTCA of these drugs in 2001 was over HK\$5 million.⁽²⁰⁾ After the UMA(A)O became effective in 2012, the amount of DTCA greatly increased, especially for those relating to blood pressure, glucose, and lipids because the advertising of these drugs are permitted if they used the prescribed permissible claims.⁽²²⁾

IMPACT OF DTCA

There is very limited literature on DTCA in Hong Kong, so the impact of DTCA was analyzed by using foreign studies and the situation of Hong Kong will be discussed based on the findings, if applicable.

Educational value

One of the most usually proposed advantages of DTCA is its educational value to the public. In US, there are surveys of public reported that about 75 percent of respondents agree that the advertisements improve their understanding of diseases and treatments, and other surveys reported that more than half of physicians agree that DTCA educates patients about health conditions and treatments.⁽²⁾ However, a FDA survey released

in 2004 reported that physicians believed advertisements did not give information about risks and benefits equally well, DTCA confuse patients about the relative risks and benefits of the drugs, and cause patients to think that the drug works better than it does.⁽¹⁾ Some content analysis studies also suggested that most DTCA lacked important information for consumers to make truly informed decisions about the benefits and risks of the drugs.⁽²⁾ Besides, a survey found that people with greater health knowledge found DTCA easier to understand and were more likely to seek further information about the advertised drug than those with less health knowledge.⁽²³⁾ This suggested that DTCA may reinforce existing knowledge rather than educate or provide new knowledge.⁽²³⁾

Unlike the United States, since there is no regulation in Hong Kong that requires DTCA to provide balanced information, DTCA may not be able to provide educational value but only act as a promotional or marketing tool. A Hong Kong survey released in 2007 reported that local doctors, especially public doctors, also tended to disagree that consumers were better informed after reading DTCA.⁽²⁰⁾

Inappropriate use of drug

DTCA may encourage people to seek medical attention for untreated conditions and prompt consumer to seek more information about previously undiagnosed medical conditions, thus appropriate drug use can be promoted. However, it may also lead to medicalization, a process where nonmedical problems are being defined as treatable illnesses.^(2,24) Besides, because of the need for adequate returns on advertising cost, DTCA tends to include relatively healthy people and promote primary prevention to wide range of people, even despite the lack of substantial evidence.⁽²⁴⁾ The result is that DTCA increases the general use or inappropriate use of prescription medicines, which are intended for treating severe diseases but not used as harmless lifestyle products, and weakens the awareness of using prescription drugs.⁽²⁵⁾

There is also evidence suggesting that DTCA can increase inappropriate prescribing. In US, a survey reported that physicians judged half of the requests prompted by DTCA were clinically inappropriate but 69 percent of them were at least partially fulfilled, with 6 percent of these judged as potentially harmful choices.⁽²⁾

If the survey data is to be projected on the situation in Hong Kong, only 22 percent of private doctors and no public doctors were asked by patients for a drug from DTCA and it was unlikely that the doctors would prescribe the drug even if asked by patients.⁽²⁰⁾ Although inappropriate prescribing may not be significant in Hong Kong, there is still a problem of self-medication since some dishonest community pharmacies dispense prescription medicines to consumers without a doctor's prescription.⁽²⁰⁾ Between 2006 to 2010, there were 58 cases of selling of Third Schedule poison without a prescription and 3 cases of selling antibiotic without a prescription reported.⁽²⁶⁾ One of the reasons of illegal sales of drug is that the Pharmacy and Poisons Ordinance (Chapter 138) only requires a community pharmacy to have a registered pharmacist to be on duty for two-thirds of the hours of each day the pharmacy is open for business.⁽¹⁸⁾ This means the pharmacy may not be under control of a registered pharmacist for the whole opening hours.

Impact on Doctor-patient relationship

It is suggested that the purpose of DTCA is to encourage patients to talk to physicians about their medical conditions and treatment options which can strengthen doctor-patient relationship. A US survey in 1999 reported that from 1997 to 1999, DTCA prompted 24 million Americans to talk to a doctor about a medical condition that had not been discussed previously.⁽²⁷⁾

When DTCA prompts a prescription request by patients, doctor should refuse any inappropriate request. However, this may affect doctor-patient relationship and some consumers would consider ending the relationship with their doctor when refused. DTCA may even cause "doctor-shopping" when consumers try to find a doctor who is willing to prescribe the requested drug.⁽²⁵⁾ From the FDA survey mentioned before, although DTCA help patients have better discussions with their physicians, 8 percent of physicians felt very pressured to prescribe the requested brand-name drug.⁽¹⁾ According to two surveys in US, 39 percent of physicians and 30 percent of public respondents agreed that DTCA interfere with good relationships between doctors and patients.^(28,29) Another survey in New Zealand reported that 69 percent of physicians agreed that they felt under pressure to prescribe advertised medications and 50 percent of physicians agreed that seeking advertised medications by patients can lead to difficulties in the doctor-patient relationship.⁽³⁰⁾

From the previously mentioned Hong Kong survey, private doctors tended to agree that the doctor-patient relationship was interfered by DTCA and believe that the relationship would be interfered if the patients were not prescribed the requested DTCA drug but public doctors tended to disagree on these two issues.⁽²⁰⁾ The fact that private doctors were more concern on the effect of DTCA on doctor-patient relationship can be explained by the economic incentives of providing patient-friendliness and preventing the loss of patients.

Economic impact of DTCA

It is suggested that DTCA can promote proper use of prescription drugs, an effective and less expensive form of health care, by prompting treatment of previously untreated conditions and by improving compliance with treatment.⁽²⁷⁾ DTCA may also encourage patients to seek medical attention which may help to manage their conditions, and reduce the number of hospital stays or surgeries and their costs.⁽³⁾

Apart from the possible reduction in cost, there is also negative financial impact from DTCA. The patients may need to spend more money and time for consultations with doctors, especially when patients visit several doctors to find a doctor who agrees to prescribe the requested drug.⁽²⁵⁾ Besides, DTCA may also promote the use of new and expensive drugs and increase the cost of drugs.⁽³¹⁾ There is a study in US estimated that during 1994 to 2005, the price of non-advertised drugs is about 44 percent lower relative to advertised drugs and broadcast DTCA caused increase in drug demand and drug price which is responsible for about 19 percent of the overall growth in prescription drug expenditures.⁽³²⁾ DTCA may also produce difficulties for government or health care providing institution in negotiations on the price of prescription drugs

as pharmaceutical companies need to recoup the costs of advertising.⁽³¹⁾ In addition, there are costs for regulation and monitoring of DTCA.⁽²⁵⁾

REGULATORY OPTIONS

Although there are some possible positive impacts of DTCA on different areas, there are more studies reporting the negative impacts of DTCA. If there is no specific regulation on DTCA, its style and content may be directed to promotional instead of educational and this may produce harmful effect to the public without its proposed advantages. The following parts will discuss on some foreign regulations as possible regulatory options for Hong Kong.

Self-regulation system - New Zealand

DTCA occurred in New Zealand because there was no specific legislation preventing it,⁽³³⁾ which is similar to Hong Kong. In fact, DTCA emerged in New Zealand in 1990, which is later than US, and was probably due to the legislation of the New Zealand Bill of Rights and to the introduction of PHARMAC. The Bill of Rights protects the freedom of speech and the PHARMAC reduced the subsidization of new drugs. These encouraged pharmaceutical companies to find new ways to promote the sales of new drugs.⁽³⁴⁾ Nowadays, regulations on DTCA in New Zealand include government laws, industry codes of practice, and a pre-vetting system.⁽²⁵⁾

The Medicines Act 1981 prohibited any false or misleading medical advertisements and any claims or suggestions that a drug will prevent, alleviate, or cure any disease, or prevent, reduce, or terminate any physiological condition specified, such as cancer, diabetes, and sexual impotence. However, the claims or suggestions that a drug will alleviate certain specified disease or reduce certain specified physiological condition, such as asthma, common cold, and gout, are not prohibited.⁽³⁵⁾ The Medicines Regulations 1984 further provide specific information requirements for drug advertisements, for example, advertisement for a prescription medicine must include certain statements to remind consumer that the medicine has both risks and benefits, and how further information of the medicine can be found.⁽³⁶⁾

The government law in New Zealand is not very restrictive for DTCA and in fact, the regulation of DTCA mainly relies on self-regulation from code of practice. For example, the Therapeutic Products Advertising Code established by the New Zealand Advertising Standards Authority gives further regulations and guidelines on top of laws. The Code includes the information that should be provided for consumer enquiry of the advertised prescription drug, such as uses, precautions, contra-indications, and adverse reactions, and statements that should be added, such as "always read the label", to encourage responsible use by consumers.⁽³⁷⁾ Moreover, there is a Therapeutic Advertising Pre-Vetting System (TAPS) established by the Association of New Zealand Advertisers which pre-vet pharmaceutical advertisements for compliance with the relevant codes and regulations before they are being accepted for placement by the media.⁽³⁸⁾ Although approval of DTCA by TAPS is not compulsory, no mainstream media would accept broadcasting the advertisements without TAPS approval.⁽²⁵⁾

One of the main advantages of this self-regulatory system is that the industry is expected to have a high level of commitment to the regulations because they are more willing to comply with rules that are established by the industry when compared to strict rules given by government.⁽²⁵⁾ Besides, this system allows flexible regulations that can be developed, changed, or updated quickly since there is no scrutiny of government agencies. Another advantage is that regulations can use language that is suitable for both the consumer and the industry, thus allowing easier understanding and resolution of disputes when compared to law. Moreover, the industry may have more related information and knowledge for developing the regulations. Lastly, there is no cost on developing and enforcing the regulations by the government.⁽³⁹⁾

Although the self-regulation system in New Zealand seems to work well with the regulations from different sectors, there are also several weaknesses in the system and one of the most important weaknesses is conflict of interest. It is argued that self-regulation cannot be effective because those responsible for reviewing advertisements can obtain vested interest in the outcome.⁽³⁴⁾ Also, it is suggested that TAPS, which comprised of members of the pharmaceutical sectors, may not be qualified to judge advertisements justly because the members may tend to consider the interest of the advertising company instead of the interest of the consumer.⁽²⁵⁾ Besides, several surveys reported that many misleading and deceiving DTCA successfully obtained approval by TAPS.⁽²⁵⁾ In addition, self-regulation system may have to face problems including lack of a representative body or commitment to enforce the code of practice and its effectiveness requires strong and committed support with active consumer participation.⁽⁴⁰⁾

In fact, concerning the negative impact of DTCA and lack of adequate regulations, healthcare community and consumer groups supported a ban on DTCA and the New Zealand government tried to ban DTCA by harmonizing with Australian standards but it was not succeeded.⁽⁴¹⁾ To conclude, the self-regulatory system may not be able to ensure a good control on the content of DTCA and eliminate the negative effect of DTCA, therefore, it may not be a suitable model to be adopted by Hong Kong.

Government regulation - United States

In US, the Congress gave the FDA authority to oversee prescription drug advertisements and pharmaceutical advertisements can be classified mainly into product claim advertisements, reminder advertisements, and help-seeking advertisements.⁽⁵⁾ The FDA have detailed requirements for each type of advertisements but in general, FDA requires DTCA to be accurate and not misleading, make claims with substantial evidence, reflect risks and benefits balance, and be consistent with the FDA-approved labeling.⁽⁴²⁾

Table 1 summarizes the content and requirements of different types of DTCA in USA.⁽⁵⁾

The Office of Prescription Drug Promotion of FDA is responsible for reviewing DTCA to ensure that the information of the advertisement is not false or misleading, reviewing complaints about suspected promotional violations, initiating

Table 1. Summary the content and requirements of different types of DTCA in USA.

Criteria	Product claim advertisement		Reminder advertisements	Help-seeking advertisements
	Print	Broadcast		
Including drug name	Yes	Yes	Yes	No
Including approved use of the drug	Yes	Yes	No	Only state a disease or condition
Risk disclosure	Use a brief summary that includes all the risks listed in the approved prescribing information of the drug	1. Present the most important risks of the drug in audio. 2. Include either adequate provision (different sources for finding the prescribing information) or brief summary	No	No
Other	-	-	Not allowed with black box warning	Not actually considered as drug advertisement and is regulated by the Federal Trade Commission instead of FDA

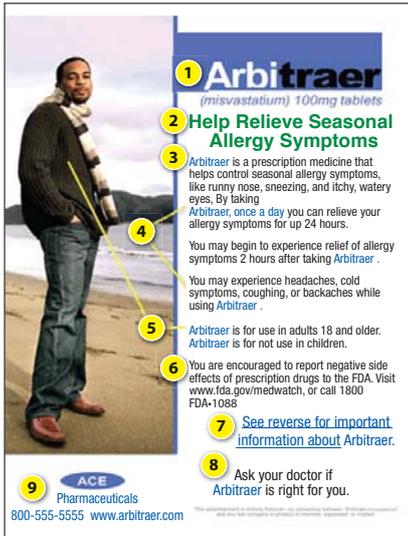


Figure 1. Correct product claim advertisement – front.⁽⁴³⁾ (1) provide brand and generic names, (2) state a FDA-approved use, (3) state the drug is given by prescription only, (4) provide fair balance of risks and benefits, (5) give approved age range and use, (6) character within the age range, (7) include required statement, (8) include the brief summary, (9) direct reader to seek doctor and (10) provide sources of further information.



Figure 2. Correct product claim advertisement – back.⁽⁴³⁾



Figure 3. Incorrect product claim of an advertisement.⁽⁴⁴⁾ Incorrect product claims in this advertisement include six misleading statements; namely (1) image of the young girl is misleading because the drug is not approved for children, (2) no studies support the claims that Arbutraer works immediately, (3) the drug is not approved to help control asthma symptoms, (4) claim is not supported by data from well-designed studies, (5) no fair balance since risks in small type size and far away from benefits and (6) no brief summary and required statement.

enforcement actions on false or misleading promotional materials, and other related works.⁽⁴⁵⁾ When the FDA determines an advertisement violates the law, it can send a letter to the drug company to explain the violation and ask the company to remove the advertisement, or to publish a corrective advertisement to fix the misimpression made by the violative advertisement, and post the enforcement letters on the Warning Letters web page. In severe case, the FDA can even seize supplies of the drug, ask for an injunction (court-enforced ban of specific activities) and bringing criminal charges against the drug company.⁽⁴⁶⁾ For a case of disseminating a false or misleading DTCA, the Food and Drug Administration Amendments Act of 2007 allowed a civil penalty of maximum \$250,000 for the first violation and \$500,000 for each subsequent violation in 3-year period.⁽⁴⁷⁾

Although DTCA is mainly regulated by the FDA, there are also industry guidelines and codes of practice that play a minor role and one example is the Guiding Principles On Direct-to-consumer Advertisements About Prescription Medicines established by the Pharmaceutical Research and

Manufacturers of America. This guideline provides further voluntary suggestions on DTCA, for example, it recommends company to include information about the availability of other options such as diet and lifestyle changes when appropriate and to submit new DTCA on television to the FDA before release,⁽⁴²⁾ although the law only requires the submission of the advertisement for a prescription drug product at the time of initial publication but not before publication.⁽⁴⁸⁾

It is suggested that the government regulation model adopted by the United States have advantages including universal coverage, compulsion, and legal enforceability over self-regulation system⁽³⁹⁾ and it can prevent the problem of conflict of interest as mentioned before. Moreover, the FDA regulation has clearer requirements for risk information and a stronger link to enforcement mechanism which cannot be found in the New Zealand model.⁽³⁴⁾

However, government regulation lose the mentioned advantages of self-regulation system and for the case of DTCA regulation by the FDA, there are other weaknesses suggested.

First, the FDA does not have the authority to require drug companies to submit advertisements for approval before they are published, thus the public may see and being influenced by misleading or incorrect advertisements before any action from the FDA.⁽⁴⁶⁾ Moreover, it is reported that a misleading advertisement was broadcast for two years before the FDA became aware of it because the FDA relies on a contracted commercial service to find television advertisements that pharmaceutical companies have failed to submit for review but the service could not identify all advertisements that are broadcast on smaller networks.⁽⁴⁹⁾ As mentioned above, the FDA can carry out different enforcement action, but regulatory letters are usually used as communication channels and principal means to prompt voluntary compliance before more severe enforcement actions.⁽⁵⁰⁾ It is mainly because companies have complied with the requests in the letters and further enforcement actions such as court actions may remove a beneficial drug from the market.⁽⁴⁹⁾ However, in 2002, the Department of Health and Human Services required review and approval of all drafts of regulatory letters by the FDA Office of Chief Counsel (OCC) before the letter could be issued and as a result, the number of issued regulatory letters were decreased. Although in 2009, the FDA announced a new policy initiative to improve the enforcement, including limiting OCC review to only draft letters of significant legal issues and considering enforcement action prior to issuance of warning letters, the number of issued regulatory letters was only increased slightly and was still lower than that before 2002.⁽⁵⁰⁾ In addition, the FDA does not restrict DTCA of new drugs, which are usually promoted heavily by DTCA, and these promotions have caused extensive use of new drugs that were later found to have serious adverse effects. One example is the recall of Vioxx (rofecoxib) in 2004 because of its cardiovascular risk, but the drug had about \$160 million DTCA spending and over \$1.5 billion in sales in 2000 after its approval in 1999.^(51,52)

In conclusion, this government regulation can strictly control the style and content of DTCA to prevent misleading and reduce the negative effect of DTCA, but this can only work with an effective regulatory system which will spend many resources and it is still questionable whether the benefits of DTCA can outweigh the risks under this regulation. Therefore, it may not be a suitable choice for Hong Kong since the cost may be greater than the benefits.

ENTIRE BAN OF DTCA AND REGULATORY CHALLENGES

DTCA is banned in most developed countries in the world and one example is the United Kingdom. In UK, advertising of medicines classified as Pharmacy Sale or General Sale List to the public is permitted if the advertisements comply with the law regulations,⁽⁶⁾ but the publication of an advertisement that is likely to lead to the use of a prescription only medicine is prohibited except for approved vaccination campaigns.⁽⁵³⁾ Although a complete ban of DTCA can prevent all negative effects of DTCA, it may not be easy to enact and execute and those countries that ban DTCA have subjected to increasing pressure to relax the restrictions.

There were repeated attempts to amend the ban of DTCA in the European Union by using patient organization and different reasons. The Directive on the advertising of medical products for human use in 1992 and the Directive on the Community

code relating to medicinal products for human use in 2001 (which is now amended by Directive 2004/27/EC), prohibit the advertising to the public of medicinal products which are available on prescription only. However, before a few months of the documentation of the 2001 Directive, an EU Commissioner proposed an amendment to the Directive on allowing for the dissemination of information of diabetes, AIDS and asthma with the reason of demands from patient groups. The Commission, however, cannot provide the names of specific patient groups that support the amendment and it was criticized for starting DTCA and was finally rejected.⁽⁵⁴⁾ During 2006 to 2008, a Commission supported Pharmaceutical Forum, which included representatives from member state, pharmaceutical federation, healthcare sector, and an industry-funded patient organization, challenged the ban again. It proposed the role of industry in providing information to patients and conducted a public consultation but this challenge was failed again.⁽⁵⁴⁾ The latest attempt was happened in 2010 which emphasized the right of the patient to receive health information instead of the right of the industry to provide information but it was also unsuccessful.⁽⁵⁵⁾

In Canada and Australia, the neighboring country of US and New Zealand respectively, are facing pressure on relaxing DTCA and was influenced by US and New Zealand. In Canada, the Food and Drugs Act prohibits the advertising of any drug to the public as a treatment, preventive or cure for diseases in Schedule A, which are usually serious diseases such as cancer and hepatitis.⁽⁵⁶⁾ The Food and Drug Regulations further prohibits the advertising of a drug in Schedule F, which are prescription drugs, to the public.⁽⁵⁷⁾ However, the government has experienced pressure for introducing DTCA since the mid 1990s. One example is the submission by Merck Frosst to Health Canada in 1996 which argue for a legal right of industry to advertise under the freedom of expression provision.⁽⁵⁸⁾ In the same year, Health Canada has published a policy statement for redefinition which approved help-seeking advertisements. In 2000, Health Canada published an administrative policy paper which allowed reminder advertisements, but when compared to United States where reminder advertisements of drugs with black box warning is banned, Canada does not prohibit the reminder advertisements of high risk drugs.⁽⁵⁸⁾ In 2008, the ban of DTCA was challenged again in the courts by a large media company but it was failed.⁽⁵⁹⁾ In addition, there is another concern that many televisions in Canada can view program provided by US satellite and cable TV, including DTCA that is illegal in Canada,⁽⁵⁸⁾ and this type of DTCA cannot be prohibited easily.

In Australia, the Therapeutic Goods Act stated that advertisement which contains a statement referring to substances included in Schedule 4 (prescription only medicine) of the Poisons Standard⁽⁶⁰⁾ should not be published,⁽⁶¹⁾ and the Medicines Australia Code of Conduct has specifically stated that prescription products must not be promoted to the public and activity directed towards the public which encourages the seeking of a prescription for a specific product is prohibited.⁽⁶²⁾ However, in 2003, the Australian and New Zealand governments signed a treaty to create a single agency regulating the registration and promotion of drugs, which is the harmonizing action as mentioned above in the part of New Zealand, and although it still allowed to maintain different policies on DTCA in the two countries,⁽⁶³⁾ it raised concerns on causing Australia to change its laws to allowing DTCA.⁽⁶⁴⁾ Also,

the Free Trade Agreement between Australia and the United States permitted pharmaceutical manufacturers to disseminate information directly to consumers via their web sites and caused a relaxation of the ban on Internet DTCA.⁽⁶⁵⁾

Asian countries are also facing pressure on relaxing their regulations on DTCA. In Korea, the Korean Pharmaceutical Affairs Law prohibits the provision of information to the public about prescription drugs except disease awareness campaigns.⁽⁶⁵⁾ Nevertheless, in the 2008, the Korean law changed to allow advertisements of prescription drugs effective against communicable epidemic diseases and the first example of DTCA on television was the prescription diarrhea vaccine RotaTeq.⁽⁶⁵⁾ In 2009, the Ministry of Strategy and Finance proposed a measure to allow DTCA in order to eradicate drug rebates to doctors and solve imbalances in prescription drugs information between consumers and professionals.⁽⁶⁶⁾ More recently, the South Korean media regulation agency has proposed allowing DTCA to enlarge the advertising market.⁽⁶⁵⁾ In Japan, although the Standards for Appropriate Advertisements of Pharmaceuticals prohibits the advertisements for prescription-only medicines to the public, the Government Revitalization Unit, which in charge of deregulating the Japanese market, proposed to abolish the ban of DTCA.⁽⁶⁵⁾

Entire ban of DTCA is a direct and easy way to prevent the negative effect of DTCA and it can be considered by the Hong Kong government. However, it is possible that proposing an entire ban will probably cause debate and opposing ideas, especially from the pharmaceutical industry, and the government will have to face the pressure on and challenge to rescind the ban.

CONCLUSION

The blooming of DTCA after the clarification of FDA requirement has caused many debates and studies on the possible effects of DTCA, such as its educational value, medicalization, prescribing habits, doctor-patient relationship, and economic impact. Since DTCA is a promotional tool, it is rational to assume that pharmaceutical companies may consider its interest over the interest of the general public and therefore it will cause danger to the health of public if DTCA is not regulated effectively. In fact, there is a loophole in Hong Kong regulations that allow certain kind of DTCA without appropriate restriction, so it is necessary for Hong Kong to develop a more complete regulation on DTCA. This paper gives an overview on some possible ruling choices including self-regulatory system, government regulation system, and entire ban, which may give more ideas on further research for the impact and regulation of DTCA in Hong Kong.

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Treatment Updates on the Hepatitis C Infection

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ABSTRACT

There are four genotypes of hepatitis C virus (HCV), genotype 1, 2, 3 and 4. Patients with different genotype have different response to treatment. New treatment strategies have been proposed for more resistant patients. Before the availability of direct acting antiviral agent (DAA), interferon and ribavirin are the mainstay of treatment. With the promising results in phase 2 and phase 3 trial, sofosbuvir is the first agent in the class of NS5B inhibitors which offer a better choice for the treatment of hepatitis C. Future development of this new class of drug and the new treatment options offer patient with better quality of life and prognosis on hepatitis carriers.

Keywords: Hepatitis C virus (HCV), sofosbuvir, NS5B inhibitor, antiviral agent, new treatment

INTRODUCTION

Hepatitis C virus (HCV) is a single-stranded RNA flavivirus that replicates within hepatocytes after transmission through percutaneous exposure. While WHO estimates that 2-3% of world population is chronically infected with HCV, there are less than 0.5% of the population in Hong Kong carry hepatitis C virus. Around 20% of those carrier will progress to cirrhosis and carry a higher risk of death caused by end-stage liver disease or hepatocellular carcinoma (HCC).⁽¹⁾ The current mainstay pharmacotherapy for HCV genotype 1 (GT-1) include pegylated interferon (PEG-IFN) and ribavirin (RBV) in combination with a direct acting antiviral agent (DAA). With the recent development of the nucleotide NS5B inhibitor, sofosbuvir, the treatment of HCV infection has come to a new era.

Hepatitis C virus (HCV) is a positive-sense RNA virus which belongs to the family of *Flaviviridae*. There are six major genotypes of HCV that have been described with distinct geographic distribution:

1. Genotype 1 (GT-1) (subtypes 1a, 1b, and 1c) accounts for 70%–75% of infections in the United States.
2. Genotypes 2 (GT-2) (subtypes 2a, 2b, and 2c) and 3 (3a and 3b) are common in the United States.

The genotype helps determine therapy duration and likelihood of responding to interferon-based therapy. (INF) In US, HCV is the leading cause of liver disease and liver transplantation and also the common cause of hepatocellular

carcinoma. In Hong Kong, the distribution of HCV genotypes among non-drug users was estimated to be 70% genotype 1, 25% genotype 6, and the remaining 5% genotype 2 and 3.⁽²⁾

The goals of HCV treatment are to (1) clear the hepatitis C virus (2) improve the quality of life and (3) prevent or delay progression to cirrhosis and hepatocellular carcinoma with recovery or improvement in liver function. The definition of successful treatment is having the virus to be undetectable for six months after treatment, a.k.a., Sustained Virologic Response (SVR). Patients achieved SVR has a low likelihood of relapse and a durable response. SVR is therefore defined as the equivalent to successful treatment of HCV.³ It is also associated with a decrease in liver-related morbidity, such as liver decompensation, liver transplantation, incidence of HCC and all-cause liver-related mortality.⁽³⁾

For many decades, IFN-based therapy has been a successful treatment for hepatitis C. However, recent studies have shown that SVR rates with INF-based combination therapy is lower in some subgroups of HCV-infected patients such as African Americans, Hispanics, patients co-infected with HIV, patients with advanced liver disease, and those who have previously failed HCV treatment.⁽⁴⁾ Therefore, new treatment option is needed for the high-risk population. An ideal agent would be a drug fulfilling the following requirements: administered once daily orally, few side-effects and drug interactions, short treatment duration, high barrier to resistance, and effective against all major HCV genotypes.⁽⁵⁾

THE FIRST HCV NS5B INHIBITOR—SOFOSBUVIR

Sofosbuvir, one of the new DAAs, is the first-in-class nucleotide NS5B inhibitor. It produces antiviral effect by inhibiting NS5B RNA polymerase enzyme, an RNA-dependent RNA polymerase. This enzyme is responsible for the synthesis of both positive-strand genomic RNA and negative-strand RNA. Sofosbuvir mimics the natural substrate of NS5B polymerase, incorporates into the growing RNA and induces a chain termination event.⁽⁶⁾ The nucleotide NS5B inhibitors target the active center of NS5B which is a highly conserved region in the viral genome. A slight change of the amino acid sequence can result in dysfunction of NS5B polymerase and a decrease in replication fitness of the virus. As the resistance profile of sofosbuvir is different from non-nucleoside NS5B protease inhibitors, it makes sofosbuvir an excellent choice to be used in combination therapy.⁽⁶⁾

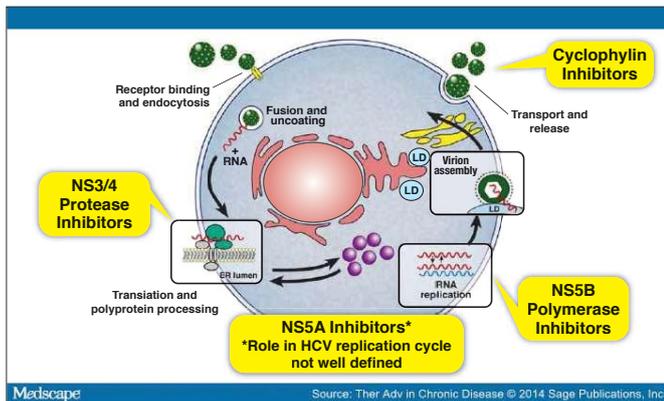


Figure 1: Drug targets in the lifecycle of the hepatitis C virus (Courtesy of Dr. Shyam Kottitil)

RECENT STUDIES

Clinical evidence on sofosbuvir is available on treatment naïve patients who have not been exposed to any HCV treatment as well as patients who developed resistance to previous treatment. In a phase 2 clinical trial, good response to treatment was seen. A 100% response rate was observed in patients randomized into sofosbuvir groups. It was advocated that sofosbuvir can have a potential role in revolutionizing the treatment for HCV.

Phase 2 Clinical Trial Results

In this phase 2 clinical trial, different combination and duration of treatment were used in HCV genotype 1, 2 or 3 patients. Forty patients with genotype 2 or 3 hepatitis C were randomized into 4 groups of 10 patients each. 10 patients were randomized into Sofosbuvir 400mg daily with Ribavirin to be dosed based on body weight for 12 weeks. The other 3 groups of patients were given the same dose of sofosbuvir, ribavirin with different treatment duration of peginterferon alfa-2a. Weekly peginterferon alfa-2a was given for a total 4, 8 and 12 weeks, respectively to these three groups of patients.

Rapid virologic response was seen in all 4 groups of patients. Serum HCV RNA levels were also not detectable 2, 4, 8, 12, 24 and 48 weeks after treatment in all 40 patients, i.e. 100% response rate were seen in this initial result. Additional two groups were then added to the study. 10 more patients treated with 12 weeks of sofosbuvir as a monotherapy and another 10 patients treated with 8 weeks of triple therapy with sofosbuvir, ribavirin and peginterferon were added. In this extension part of the study, 6 out of the 10 patients in the sofosbuvir monotherapy group had a Sustained Virologic Response (SVR) at 12 and 24 weeks after treatment, whereas all 10 patients on triple therapy for 8 weeks had a SVR at week 24. Meanwhile, 35 patients with HCV genotype 1 were also recruited to the study and given 12 weeks of sofosbuvir and ribavirin. 25 of them were treatment naïve and 10 of them had failed previous treatment. 21 out of 25 treatment naïve patients had a SVR at 24 weeks whereas 1 out of 10 patients who had failed previous obtained SVR at 24 weeks. In fact, all patients with HCV genotype 2 or 3 treated with 12 weeks of sofosbuvir had a sustained response to treatment in combination of ribavirin and different schedule of peginterferon. This is the first study to show a 100% response. Further research was then carried out to proof the efficacy of this new class of drug although the 100% result was not seen in monotherapy and patients with HCV genotype 1.

NEUTRINO AND FISSION TRIALS⁽⁸⁾

Two phase 3 studies were then carried out to prove the clinic efficacy of sofosbuvir. NEUTRINO study was a single group study with HCV genotype 1, 4, 5, 5 and 6 patients treated with sofosbuvir, ribavirin and peginterferon alfa-2a for 12 weeks. 327 patients were enrolled in the study and 295 of them (90%, 95% confidence interval, 87-93) had a SVR 12 weeks after treatment. That is significantly different from the historical response rate of 60%.

Fission study was a randomized controlled trial in patients with HCV genotype 2 or 3. One group of patients was treated with 12 weeks of sofosbuvir plus ribavirin and another arm treated with 24 weeks of peginterferon plus ribavirin. Non-inferiority test was performed to compare the difference of responses of two groups. At 4 weeks and 12 weeks after the treatment, both groups had a SVR of 74% and 67% respectively. There was a statistical significant difference between two groups in terms of non-inferiority ($p < 0.001$). In another word, both groups are not inferior to each other. As the efficacy of both treatment regimens was proven to be comparable, the difference of side effect profile would determine the regimen to be used. Common mild side effects like fatigue, nausea and vomiting are more common in the interferon group. Toxicities that are common to interferon treatment like influenza-like symptoms, fever and depression are also observed more often in interferon group.

Besides the favorable efficacy in combination therapy of sofosbuvir group, there are still some findings that can support the use of sofosbuvir. There are 102 patients relapsed in the sofosbuvir treatment in both NEUTRINO and FISSION studies. Deep sequencing analysis of the samples was performed after the treatment. No resistance-associated variants were found in these samples. Lack of documented resistance made sofosbuvir an attractive choice for hepatitis C treatment.

POSITRON and FUSION Trials

In these two trials, HCV genotype 2 or 3 infected patients who were not suitable for interferon therapy or did not respond to interferon therapy were recruited. The POSITRON trial was a randomized controlled study comparing 12 weeks of sofosbuvir plus ribavirin treatment with placebo. SVR was measured 12 weeks after treatment, 78% of patients in the treatment obtained a SVR 12 weeks after treatment while 0% in the placebo group obtained SVR.

In FUSION study, only patients who failed previous interferon treatment were recruited. Patients were randomized into 12 weeks or 16 weeks of sofosbuvir and ribavirin treatment. The rate of SVR in patients treated for 12 week was 50% where the rate was 73% in the 16 weeks treatment group. They are both significantly higher than the historical control of 25%. It showed that a longer treatment period is necessary for patients who failed previous interferon treatment.

In these two studies, sofosbuvir plus ribavirin is a possible treatment option for HCV genotype 2 or 3 infection for whomever not suitable for interferon therapy. Patients who failed previous treatment may benefit from longer treatment with sofosbuvir and ribavirin. There was no established treatment for this group of patients previously. These two studies advocated the role of sofosbuvir plus ribavirin in the second line treatment for HCV infection.

The AASLD Guideline and IFN-free DAA Therapy

Combining the results of these four landmark studies, the AASLD and IDSA has published new guidelines in which sofosbuvir is recommended for those patients who need initiating treatment for HCV Infection and for those who have experienced relapse after prior PEG-INF/ribavirin. (Table 1).⁽⁹⁾ Based on the guideline, IFN-free sofosbuvir therapy is recommended for those infected with GT-2 and GT-3 and for GT-1 and GT-4 if they are intolerant or ineligible to be treated with IFN. Of note, the use of sofosbuvir specifically includes patients who have the most urgent need for treatment due to advanced disease and increased risk of death including those with HCC, those awaiting liver transplantation, and patients with HIV-1 co-infection.⁽⁹⁾ However, sofosbuvir is not approved for patients with severe renal impairment (estimated glomerular filtration rate less than or equal to 30 mL/min/1.73 m²) or end stage renal disease.⁽¹⁰⁾ Indeed, no dosage adjustment of sofosbuvir is required for patients with hepatic impairment. The safety and efficacy have not been established in children and adolescents aged <18 years. Due to limited data available at present, it is suggested that sofosbuvir should be avoided during pregnancy and breastfeeding.⁽¹⁰⁾

Table 1. Summary of recommendations for patients who are initiating therapy for HCV infection or who experienced relapse after prior PEG-INF/ribavirin therapy, by HCV genotype⁽⁹⁾

Genotype	Recommended	Alternative	NOT Recommended
1	IFN eligible: SOF + PEG/RBV x 12 weeks IFN ineligible^[1]: SOF + SMV ± RBV x 12 weeks	IFN eligible: SMV x 12 weeks + PEG/RBV x 24 weeks* IFN ineligible^[1]: SOF + RBV x 24 weeks	TVR + PEG/RBV x 24 or 48 weeks (RGT) BOC + PEG/RBV x 28 or 48 weeks (RGT) PEG/RBV x 48 weeks Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis ^[2] with PEG or SMV
2	SOF + RBV x 12 weeks	None	PEG/RBV x 24 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV
3	SOF + RBV x 24 weeks	SOF + PEG/RBV x 12 weeks	PEG/RBV x 24-48 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV
4	IFN eligible: SOF + PEG/RBV x 12 weeks IFN ineligible^[1]: SOF + RBV x 24 weeks	SMV x 12 weeks + PEG/RBV x 24-48 weeks	PEG/RBV x 48 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR or BOC
5 or 6	SOF + PEG/RBV x 12 weeks	PEG/RBV x 48 weeks	Monotherapy with PEG, RBV, or a DAA Any regimen with TVR or BOC

Table 2. Pharmacokinetics profile of sofosbuvir⁽¹¹⁾

Absorption	Time to peak: 0.5 to 2 hours post dose
Metabolism	Hydrolysis, phosphorylation, dephosphorylation
Distribution	61–65% bound to human plasma proteins
Elimination	Renal clearance (80% active metabolite recovered in urine)

Safety Profile and the Cost

Regarding the safety profile of sofosbuvir, it is a substrate of the P-glycoprotein (P-gp) transporter; therefore, potent inducers may decrease sofosbuvir plasma concentrations and potentially lead to treatment failure. As a result, the following drugs should not be co-administered with sofosbuvir e.g. carbamazepine, phenytoin, phenobarbital, oxcarbazepine, rifampicin, rifabutin and St. John's wort.⁽¹⁰⁾ Of note, there are no adverse drug reactions specific to sofosbuvir have been identified. The most common adverse effects observed were fatigue, headache, nausea and insomnia and anemia, all of which are consistent and comparable with peginterferon alfa and ribavirin.¹⁰ While Sofosbuvir offers the advantage of IFN-free therapy with low pill burden, the wholesale cost of a 28 day supply of sofosbuvir is HK\$196,000. i.e. HK\$7,000 per tablet, the cost has created concerns about justifying a treatment course with sofosbuvir. Clinicians must consider the cost per SVR rather than just the acquisition cost of sofosbuvir. Patient who fails standard treatment will eventually either have to be treated again with expensive antivirals or suffer the cost of living with decompensated cirrhosis or liver transplantation. In addition, this is the first all-oral, IFN-free regimens, all of which could potentially outweigh the current cost of treatment.

Author's background

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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.pcccchk.com) to fill in their answers there.)

1. Which of the followings are the common side effects of traditional peginterferon-ribavirin regimen?

- (i) Anemia
 - (ii) hyperpigmentation of tongue
 - (iii) teratogenicity
 - (iv) Depression
- A. (i), (ii) and (iii)
B. (i), (iii) and (iv)
C. (ii), (iii) and (iv)
D. All of the above

2. Which of the following situation when peginterferon is safe to be used?

- A. Male with a female pregnant partner
- B. History of tuberculosis infection
- C. Psychosis episode
- D. Active vasculitis

3. Which one of the followings is NOT the goal of hepatitis C treatment?

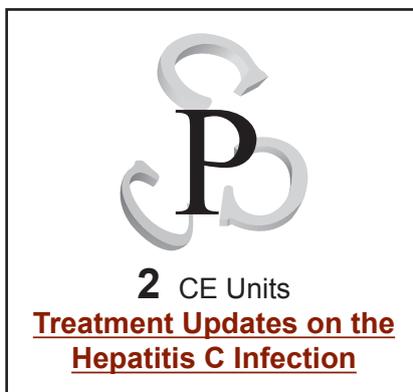
- A. Eradicate of hepatitis C virus
- B. Normalise the bilirubin level
- C. Improve the quality of life
- D. Prevent progression to cirrhosis and liver cancer

4. Where is the site of action of sofosbuvir?

- A. DNA methyltransferase
- B. RNA polymerase
- C. DNA topoisomerase
- D. RNA transcriptase

5. What is the SVR after 12 weeks of treatment in the NEUTRINO study?

- A. 50%
- B. 75%
- C. 90%
- D. 95%



6. What is the SVR after 12 weeks of treatment in the FISSION study?

- A. 53%
- B. 67%
- C. 82%
- D. 90%

7. Which of the following trials recruited patients who have failed previous treatment only?

- A. NEUTRINO
- B. FISSION
- C. POSITRON
- D. FUSION

8. Which of the following situation when sofosbuvir is contraindicated?

- A. Estimated creatinine clearance < 10ml/min
- B. AST > 3 x ULN
- C. ALT > 3 x ULN
- D. Total bilirubin > 20 mcml/L

9. According to the AASLD guideline, interferon-free sofosbuvir therapy CANNOT be used in which of the following patient?

- A. Genotype 1 infection without previous treatment
- B. Genotype 2 infection
- C. Genotype 3 infection
- D. Genotype 4 infection who cannot tolerate interferon-based treatment

10. Which of the following drug can potentially reduce the plasma concentration of sofosbuvir?

- A. Valproate Sodium
- B. Pantoprazole
- C. Carbamazepine
- D. Lamivudine

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 213(D&T)

Overview of Medications for Solid Organ Transplantation

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

Rational Drug Design of Neuraminidase Inhibitors as Novel Anti-Influenza Agents

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ABSTRACT

Influenza is a highly contagious infection of the respiratory tract and transmitted by droplets containing influenza viruses A, B or C. Spread of these pathogenic viral particles is responsible for the considerable global pandemic disease. In the prophylaxis and treatment of influenza, neuraminidase (NA), the enzyme cleaving a terminal sialic acid (SA) residue from glycoconjugates enabling release of the virion from infected cells, has been considered an ideal target for designing promising therapeutics. One of such potent and specific NA inhibitors is oseltamivir (Tamiflu[®]) which is a transition-state analog of SA derived from computer-aided rational drug design. Baicalein, a naturally-occurring polyphenolic constituent of *Scutellaria baicalensis* Georgi and other forage, has also been shown an important phytochemistry of interest as protectants against flu and other diseases. We report herein their design and relevant synthetic approaches toward novel anti-influenza activities with NA as target.

Keywords: Influenza, viral disease, rational drug design, neuraminidase inhibitor, sialic acid, oseltamivir, baicalein analogs, *Scutellaria baicalensis* Georgi

INTRODUCTION

Influenza or “flu” is an acute infection of the respiratory tract caused by influenza viruses A, B or C, which occur worldwide and are responsible for causing epidemics and pandemics that affect millions of people every year. It is highly contagious and occurs mainly in the late fall, winter, or early spring. It can be spread from person-to-person through mists or sprays of infectious respiratory secretions caused by coughing and sneezing. In the US alone, approximately 114,000 hospitalizations per year have been attributed to influenza, and about 20,000 Americans die because of influenza or influenza related pneumonia each year. Over 90% of the deaths occur in persons aged 65 years and older. In the UK the highest incidence is between December and May, with a

peak during February and March. Hence, influenza epidemics are a major public health concern because of the economic and productivity lost linked to this viral infection are staggering. Even though mortality is not the outcome of influenza infection, the disease produces significant morbidity that ranges from transient, disabling symptoms to secondary bacterial infections e.g. sinusitis, bronchitis, and pneumonia. It dramatically increases workloads for physicians in emergency room and burden on healthcare resources.

Symptoms of flu

The symptoms of influenza include fever (usually 100 to 103 °F in adults, and sometimes higher in children), headache, dry cough, sore throat, nasal congestion, chills/sweats, muscle or joint pain, fatigue, weakness and body aches etc. These symptoms reflect that the immune system of the infected person is working very hard to fight against the virus. They occur because cytokines have been produced by activating the immune cells.

TREATMENT OF INFLUENZA

Figure 1 summarizes the life cycle of the influenza virus and the sites of drug action.⁽¹⁾ Amantadine and derivatives block the penetration of the influenza virus into host cells. Recent studies suggest that this drug is a M2 proton-selective ion channel inhibitor; therefore, it blocks the conformational change of hemagglutinin and the subsequent release of RNP. Virus RNA (vRNA) in the host cells can be replicated via complementary RNA (cRNA) synthesis or used as a template for protein synthesis mediated through mRNA synthesis. Replication of vRNA can be inhibited by ribavirin, an inosine-5'-monohydrate dehydrogenase (IMPDH) inhibitor. The last measurement can be taken is using neuraminidase inhibitors, such as oseltamivir and zanamivir to terminate the release of the newly formed virions from the infected cells and thus prevent their spread and further damage.

The control of influenza infection was limited until the introduction of oseltamivir in 1999.⁽²⁾ Prior to this, the first

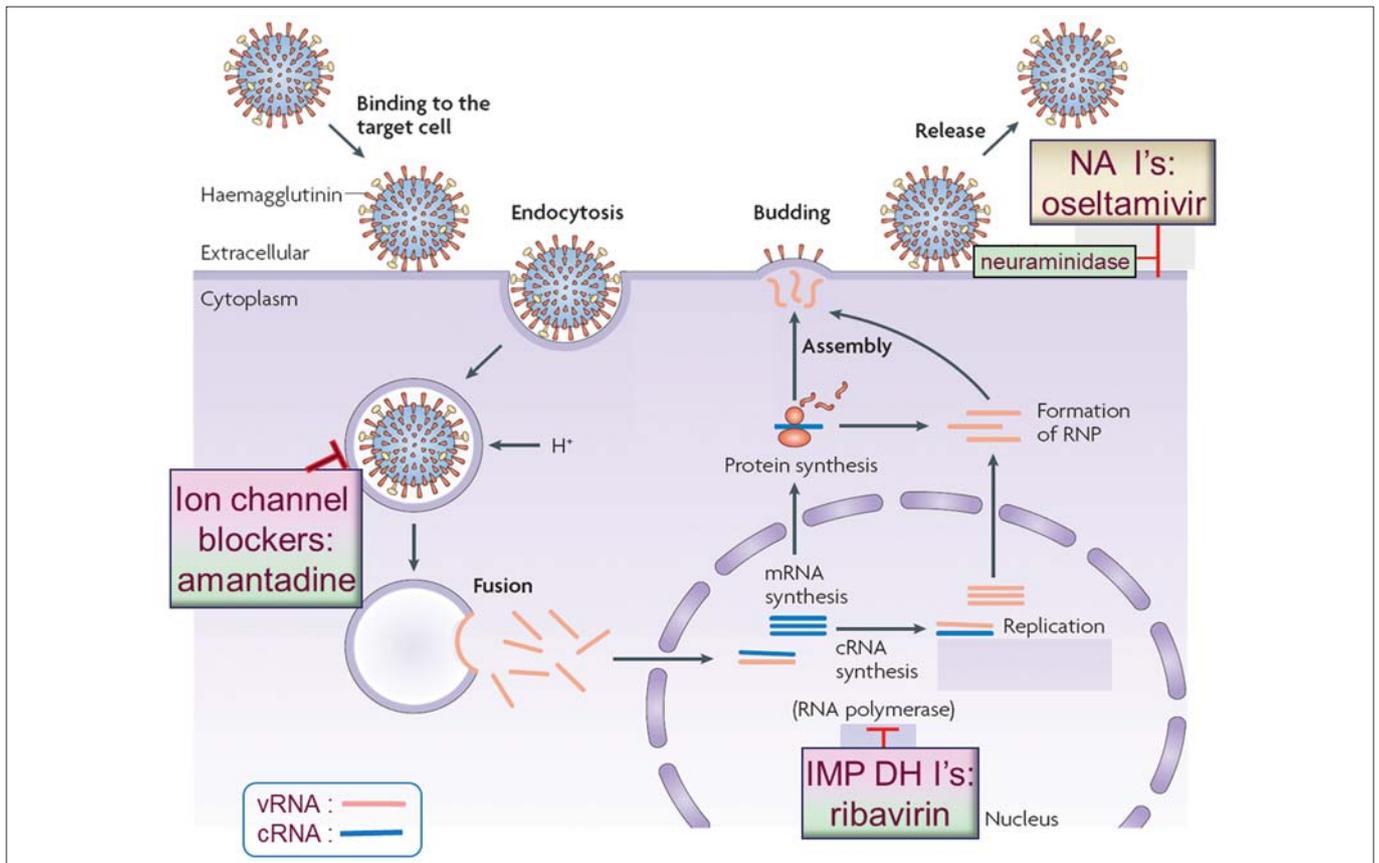


Figure 1. Life cycle of influenza virus and the sites of drug action. [modified from von itzstein⁽¹⁾]

option was the usage of vaccines. However, vaccine is not effective because influenza viruses undergo frequent antigenic variation in the two surface antigens, namely hemagglutinin and neuraminidase. Thus, development of effective vaccines against influenza or new formulation is required each year.

Alternatively antiviral drugs, such as amantadine and rimantadine, both M2 ion channel inhibitors, were used for treatment of influenza infected individuals. These drugs, however, revealed limited usage because they have adverse side effects, mainly on the CNS, and lack activity against influenza virus B. Consequently, it is necessary to develop safer and more effective medicines for controlling and treating the influenza.

DESIGN OF NEW NEURAMINIDASE INHIBITORS

Design and synthesis of zanamivir

Influenza virus (A and B) adopt a unique replication strategy by using one of its surface glycoproteins, neuraminidase, to cleave off the terminal sialic acid, to egress from the cells, after the viral replicative cycle has been completed. Therefore, elution of the newly formed virus particles from the cells required the action of neuraminidase and thus blockage of this elution process by neuraminidase inhibitors may prevent the spread of the progeny virions to other host cells. Thus, the objective of drug design against influenza should be to design potent inhibitors of the influenza neuraminidase enzyme.

To achieve this objective, rational drug design accompanied with the available high resolution X-ray crystal structures of sialic acid was applied. To achieve the objective, the structures of influenza neuraminidase, sialic acid and their complex should be identified and studied by the high resolution X-ray crystal structures. The result is shown in Figure 2.

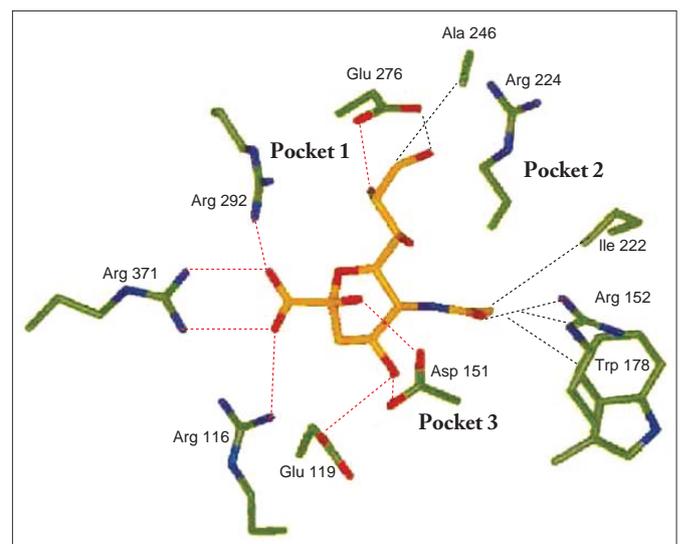


Figure 2. Key Interactions between neuraminidase active site residues and sialic acid.

This Figure shows that the active sites of neuraminidase, which can be divided into three major binding pockets, namely pocket 1, 2 and 3. These pockets are strictly

conserved with the sialic acid because the structure of each pocket is different; i.e. pocket 1 is a highly polar, pocket 2 is a hydrophobic and pocket 3 is a hydrophilic residues. Hence, each pocket interacts differently with a substrate required for activating the neuraminidase. These highly conserved and multi-interacting arrangements create difficulties for designing new neuraminidase inhibitor.

To design a new drug, data from X-ray crystallography analysis of the sialic acid/neuraminidase complex is very useful. It was found that the X-ray structure of a deformed sialic acid in the complex possess a very similar structure with the Neu5Ac2en, which is a chemical containing a pyranose ring into planar structure around the ring oxygen. The structure of this compound labelled with a red arrow is shown in **Figure 3**.

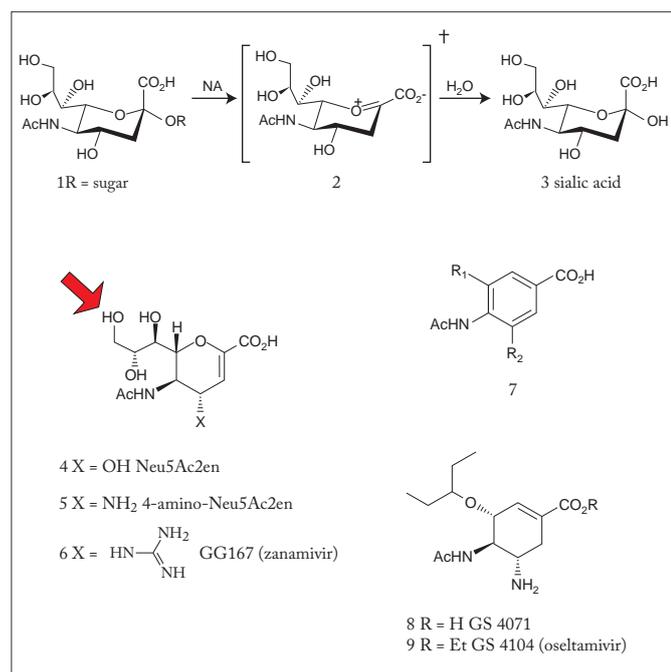


Figure 3. The structure of different chemicals in the development of neuraminidase inhibitors.

Based on the X-ray crystallographic data of Neu5Ac2en, zanamivir (compound **6** in the **Figure 3**) was discovered and synthesized. This drug exhibited potent antiviral activity against a variety of influenza A and B and was approved for the treatment of influenza infection in the U.S. and Europe while in Australia, it was named as Relenza®.

Development of other neuraminidase inhibitors

A major problem for the usage of zanamivir is that its administration has to be via inhalation. To overcome this problem, Cyclohexene Scaffold Approach was proposed for the development of potent orally active neuraminidase inhibitors. It is based on the cyclohexene scaffold shown at blue arrow in **Table 1**. It was revealed that the cyclohexene ring is chemically and enzymatically stable and the structure and positioning of the interacting groups is more important. Cyclohexene ring, therefore, simply provides a stable template for chemical modifications of substituents for optimizing its biological activity.⁽³⁾

Table 1. Influenza Neuraminidase Inhibition			
Compound	R	Enzyme IC ₅₀ (nM)	
		flu A ^a	flu B ^b
11	H-	6300	ND ^c
12	CH ₃ -	300	ND ^c
13	CH ₃ CH ₂ -	2000	185
14	CH ₃ (CH ₂) ₂ -	180	15
15	CH ₃ (CH ₂) ₃ -	300	215
16	CH ₃ (CH ₂) ₅ -	150	1450
8	(CH ₃ CH ₂) ₂ CH-	1	3
17	(S)	0.3	70
18	(R)	12	35
19		1	2150

^aA/PR/8/34 (H1N1); ^bB/Lee/40; ^cnot determined

In the design of orally active antiviral drug, the main focus is to properly balance the lipophilicity and the water solubility of the drug for oral absorption from the intestinal tract. This was achieved by addition of a lipophilic alkyl group for potentially enhancing of overall oral bioavailability. After massive screening (compounds 11-19 in the **Table 1**), GS 4071 was discovered and its X-ray crystallographic structure revealed that the binding mode was similar to that of Neu5Ac2en. Its binding sites conserved the active sites of the neuraminidase and are shown in **Figure 4**.

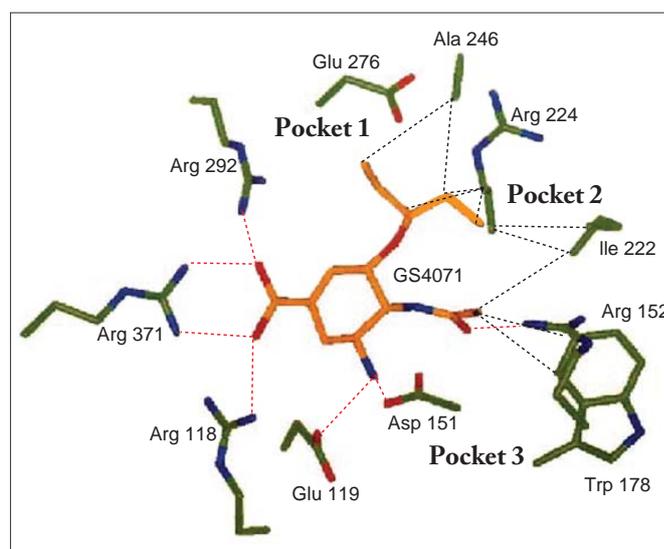


Figure 4. Interactions between neuraminidase active site residues and GS 4071.

Influenza Neuraminidase Inhibitory chemicals⁽⁴⁾

Although GS 4071 was designed for the development of an orally active influenza neuraminidase inhibitor and its

studies on influenza neuraminidase inhibition is superior, the studies of vivo activity shown that GS 4071 is very low in oral bioavailability. It was only about 5% in rats. As a result, there is a need for modification of the GS 4071 to increase the oral bioavailability.

Oseltamivir

Oseltamivir was discovered as an ethyl ester prodrug of GS4071. It contains the structure of GS4071 with H in carboxyl group replaced by ethyl ester as shown in the **Figure 5**. However, based on this difference in structure, oseltamivir possesses a much better oral bioavailability than GS4071. *In vivo* studies revealed that the oral bioavailability of oseltamivir was ~ 30% in mice, ~ 70% in dog and ~ 80% in human. Oseltamivir is known as a prodrug of GS 4071 because it is converted to the GS 4071 after absorbed in the body.

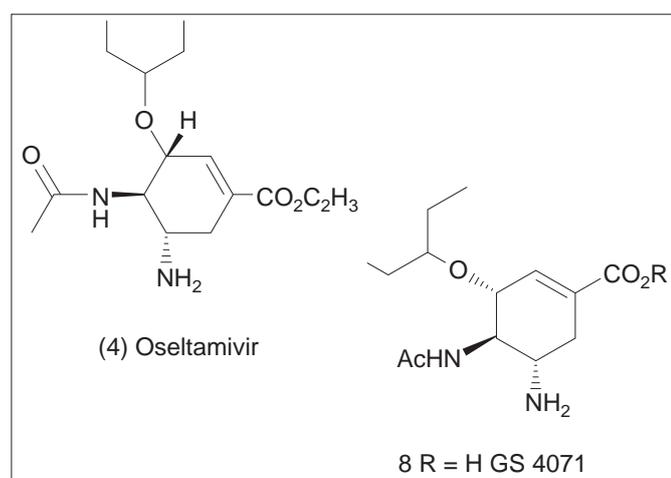


Figure 5. Chemical structure of oseltamivir and GS 4071⁽⁵⁾

Oseltamivir phosphate, with the brand name “Tamiflu®”, was developed by Hoffmann-La Roche Inc, which is approved by the US FDA as an oral anti-viral drug for the treatment of uncomplicated influenza in patients one year and older whose flu symptoms have not lasted more than two days. The drug is also approved for the prevention of influenza in adults and adolescents older than 13 years. It is available as a capsule containing 75 mg of oseltamivir for oral use, and also as a powder for oral suspension, containing 12 mg/ml oseltamivir base. Besides the active ingredient, Tamiflu® capsules also contain pregelatinized starch, talc, povidone K 30, croscamellose sodium and sodium stearyl fumarate.

The chemical structure of oseltamivir phosphate is (3R,4R,5S)-4-acetylamino-5-amino-3-(1-ethylpropanoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula is C₁₆H₂₈N₂O₄ (free base) and the molecular weight is 312.4 for the free base and 410.4 for the phosphate salt. It is an ethyl ester prodrug requiring ester hydrolysis for conversion to the active form, oseltamivir carboxylate (Ro 64-0802, GS4071). It is a potent and selective inhibitor of the neuraminidase; a glycoprotein essential for replication of influenza A and B viruses. In other words, oseltamivir can reduce the severity of symptoms and shorten the duration of flu episodes, by interfering with the synthesis

of the viral enzyme neuraminidase, which is needed for the virus to infect cells in the respiratory tract and elsewhere in the body. The drug affects only certain susceptible strains of the influenza type A or B viruses.

In the animal and clinical studies of the drug development, the result indicated that the oral administration effectively delivers to respiratory tract in animals and it is effective in preventing experimental influenza virus infection. Therefore, oseltamivir (Tamiflu™) was approved in October 1999 by the U.S. Food and Drug Administration for use as the first orally administered neuraminidase inhibitor for the treatment of influenza infection in adults.

Industrial synthesis of the key precursor of the drug oseltamivir phosphate

Oseltamivir phosphate (**9**) is a prodrug of the potent neuraminidase inhibitor and targeted for use as an orally active antiviral compound for prevention and treatment of influenza infections.⁽⁵⁾ During the course of synthesis study as shown in **Figure 6**, it was found that (-)-shikimic acid (**23**) represents an ideal alternative raw material for the synthesis of epoxide **10** due to the fact that the double bond is already present in the correct position. Moreover, epoxide **10** is the main key precursor for the manufacture of oseltamivir phosphate (**1**). However, because of the commercially confidential information, there is no synthetic procedure provided.

As suppliers were identified which were able to manufacture (-)-shikimic acid on a large scale either by means of fermentation or by extraction of star anise or ginkgo leaves, an efficient synthesis of ketal intermediate compound **8** from this natural product was developed. Depending on the source, batches of (-)-shikimic acid (**23**) had assays ranging from 85 to 99% and very different impurity profiles. Thus, a process had to be developed able to cope with variable quality. We evaluated two routes: the direct conversion to pentylidene ketal **8** and the route via acetamide **7**. The acetamide route was preferred to the pentylidene ketal route, although longer by one step. Acetamide **7** is a highly crystalline compound which can be purified efficiently. In contrast, the intermediates of the pentylidene route **25** and **8** are oils and had to be carried through in crude form. Hence, purification was only possible at the stage of epoxide **10**. The resulting epoxide **10** often did not meet the quality requirements and had to be reprocessed. Furthermore, the overall yield decreased from 65 to 45%. Therefore, the direct route through intermediate **25** was dropped.

(-)-Shikimic acid (**23**) was esterified under acidic conditions. With H₂SO₄ (0.05 equiv) or TsOH (0.1 equiv.) in boiling EtOH the reaction proceeded slowly and even after 20 h, 5% starting material remained unreacted. Better results were achieved with EtOH/SOCl₂. After 3 h at boiling temperature, <2% of **23** was detected. The solvent was exchanged from EtOH to EtOAc and crude ethyl shikimate **24** was treated with 2,2-dimethoxypropane in the presence

of TsOH to give ketal **26**. MeOH was removed by azeotropic distillation at 35 °C under reduced pressure. Mesylation of **26** was accomplished in EtOAc. The normal aqueous workup was deemed unsuitable for technical scale due to the formation of emulsions, which were difficult to break. A practical solution for this problem was found whereby the crude reaction mixture was filtered on a basket centrifuge to remove Et₃NHCl and insolubles. The filtrate was concentrated and the residual crude product crystallized from MeOH and yielded **7** in 82% yields with an assay of 97-99%. Mesylate **7** was converted to epoxide **10** as shown in diagrams. It was isolated with an overall yield of 63-65% from shikimic acid (**23**) and had an assay of at least 99%.

The demand for drug substance increased substantially as it entered phase II and III clinical trials. To enable large-scale production of epoxide **10**, each step of the synthesis requires further improvement. Special focus was directed to the dehydration reaction to form the shikimic acid derivative **7** and the reductive ketal opening to form hydroxyether **9**. Furthermore, the development of synthesis of epoxide **10** from (-)-shikimic acid (**23**) can meet these targets and which is the effective and desirable industrial synthesis of the key precursor of the drug oseltamivir phosphate (**1**).

Organic synthesis of oseltamivir

The step and intermediate compounds for the synthesis of oseltamivir are shown in **Figure 6**.

Clinical uses of oseltamivir

This medicine contains the active ingredient, oseltamivir phosphate, which is a neuraminidase inhibitor. It is used to treat and prevent infection with the influenza virus (flu).

Oseltamivir works by binding to the neuraminidase on the surface of the virus particles, and stopping it from working. When the neuraminidase helper is blocked in this way it means that newly formed viral particles cannot be released from the infected cells. This prevents the flu virus from spreading and infecting other cells. Oseltamivir therefore confines the infection to a smaller area. This makes the symptoms of the infection less severe and also makes it easier for the body's immune system to kill the virus. The medicine has been shown to reduce the duration of the illness by approximately one day, and to reduce the risk of developing flu-related complications, such as chest infections that require antibiotics.

Side effects of oseltamivir

Medicines and their possible side effects can affect individual people in different ways. The following are some of the side effects that are known to be associated with this medicine. Because a side effect is stated here, it does not mean that all people using this medicine will experience that or any side effect like rash, abdominal pain, vomiting and nausea. It is unlikely that this medicine will interact with other medicines but the manufacturer of this medicine states that it should be used with caution in people who are taking the following medicines:

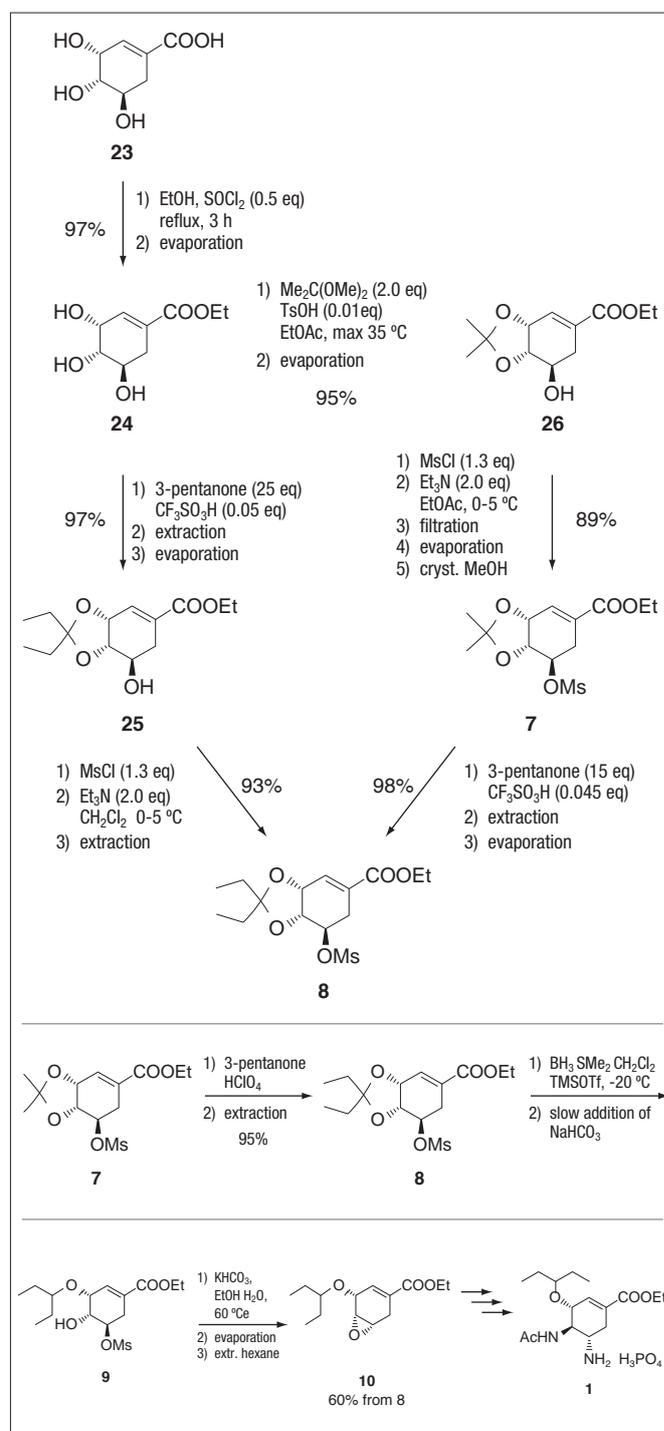


Figure 6. Steps and intermediate compounds of the synthesis of oseltamivir (**1**).

chlorpropamide, methotrexate, phenylbutazone. This medicine is also not recommended for people with severely decreased kidney function as it may decrease the kidney function. Pregnancy and breastfeeding mother should also consult the doctor before taking it.

Synthesis of Baicalein Analogs as Novel Anti-influenza Agents

Baicalein, a naturally-occurring polyphenolic constituent of *Scutellaria baicaensis* Georgi and other forage,⁽⁶⁾ has been shown an important phytochemistry of interest as protectants

against flu and other diseases and thus revealed the true impact of the treatments. The design and relevant synthetic approaches toward novel baicalein analogs as effective anti-influenza agents with NA as target have been investigated by Lee et al.⁽⁷⁾ Briefly, reaction of 3,4,5-trimethoxyphenol with equimolar substituted cinnamoyl chlorides gave chalcones as the key intermediates. Intramolecular oxidative cyclization with I₂/DMSO followed by demethylation afforded, depending on the controlled conditions, various baicalein analogs in excellent yields after column chromatography. Similar manipulations could readily produce diverse flavonoids.⁽⁸⁾ Lee reported that some of their synthetic compounds demonstrated very potent activity, in vitro, against H1N1 viruses. Further investigations on their mechanisms of action aided by molecule modeling study proved to be inhibition of NA; however, in more or less different manner from oseltamivir. This might explain the reason why they still sustain noticeable activity even against the oseltamivir-resistant strains. Recently, Lee et al reported that modification of baicalein, especially with the B-ring substituted with bromine atoms, could further maximize its activity.⁽⁶⁾ Some synthetic baicalein analogs even demonstrated much higher potency than oseltamivir against H1N1 Tamiflu-resistant (H1N1 TR) virus and with more favorable selectivity. The flavonoids having both not-naturally-occurring bromo-substituted B-rings and appropriate hydroxyls positioning on the A-rings might be critical in determining the activity and selectivity against H1N1 TR infected influenza viruses.

CONCLUSION

Neuraminidase inhibitors still remain part of the anti-viral mainstream by specifically inhibiting neuraminidase, the key enzyme responsible for release of newly formed virions to invade host cells. The advent of seltamivir and zanamivir, the two major specific neuraminidase inhibitors, represent a new generation of antiviral agents associated with excellent efficacy and specificity. It can be expected that, in future, the availability of brand new neuraminidase inhibitors would depend primarily on the successful application of computer-aided drug design and practical synthetic approaches. Novel anti-viral drugs with activity against Tamiflu-resistant virus and with more favorable selectivity will doubtless a therapeutic trend, which might be obtainable by active investigation on natural resources, including traditional Chinese medicines.

Author's background

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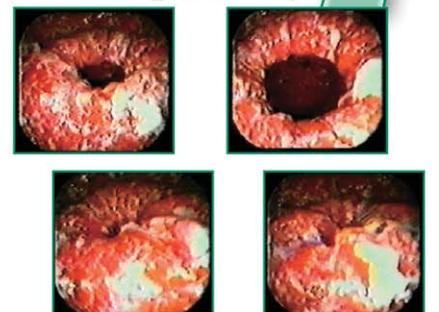
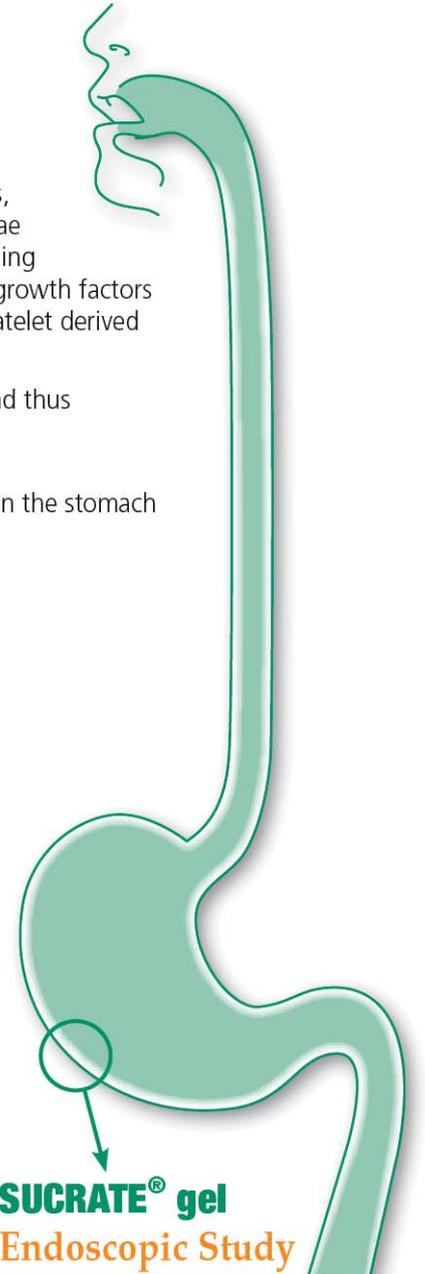
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Cosentino F. et al., Società Italiana di Endoscopia Digestiva, VII Simp. Naz, Napoli, 1992

An Evidence-based Review on the Efficacy of Nutraceuticals for Migraine Prophylaxis in Adults

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ABSTRACT

Migraine is a prevalent neurological disorder and one of the leading causes of disability worldwide. There are a variety of medications proven effective for migraine prevention but they are associated with safety concerns and relatively high costs. As a result, nutraceuticals have become increasingly popular among patients with migraine. This article reviews the clinical efficacy of seven widely available nutraceuticals for migraine prophylaxis. Among them, butterbur appears to be efficacious in reducing the frequency, intensity and duration of migraine episodes. While certain formulations of feverfew and magnesium have shown promising benefits, there is inadequate evidence to draw a firm conclusion. More clinical trials are also needed to support the use of riboflavin, coenzyme Q10, alpha-lipoic acid and melatonin for this indication. Pharmacists should take the initiative to make patients and physicians aware of the up-to-date evidence on the efficacy and safety of these nutraceuticals.

Keywords: Butterbur, feverfew, magnesium, coenzyme Q10, alpha-lipoic acid, melatonin, migraine, nutraceutical, riboflavin

INTRODUCTION

Migraine is an incapacitating neurological disorder with two major subtypes. Migraine with aura, formerly known as classic migraine, is characterised by the transient focal neurological symptoms that occur before and/or during the headache episode. The more common subtype is migraine without aura, which is also called common migraine.⁽¹⁾ The diagnosis of migraine requires a collection of clinical features (**Table 1**) based on the most updated criteria of the International Headache Society (IHS). Currently, migraine is one of the most prevalent diseases, affecting over one billion people worldwide.⁽²⁾ The one-year prevalence rates of migraine were between 8.4% and 12.7% in Asia, which were in the low range of those reported in Western countries.⁽³⁾ In 1998, a population-based telephone survey was conducted in Hong Kong and revealed that 12.5% of people aged 15 years or older suffered from migraine within the previous 12 months.⁽⁴⁾

A more recent nationwide study showed a prevalence rate of 9.3% in China, with a female-to-male ratio of 2.15:1.⁽⁵⁾ In addition, migraine can have a devastating impact on patients' social lives, productivity in the workplace, and overall quality of life.⁽⁵⁻⁸⁾ According to the Global Burden of Disease Study 2010, migraine ranked as the eighth leading cause of disability, as measured in years lived with disability (YLD).⁽²⁾ In China, the annual total costs associated with migraine were estimated to be USD 47.8 billion, accounting for 1.1% of gross domestic product (GDP) in 2008.⁽⁵⁾

Table 1. Diagnostic criteria for migraine based on the International Classification of Headache Disorders, third edition (beta version) (ICHD-3 beta)

Migraine with aura	Migraine without aura
A. ≥ 2 attacks fulfilling criteria B and C	A. ≥ 5 attacks fulfilling criteria B–D
B. ≥ 1 of the following reversible aura symptoms: (1) visual (2) sensory (3) speech and/or language (4) motor (5) brainstem (6) retinal	B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated) C. Headache has ≥ 2 of the following 4 characteristics: (1) unilateral location (2) pulsating quality (3) moderate or severe pain intensity (4) aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
C. ≥ 2 of the following 4 characteristics: (1) ≥ 1 aura symptom spreads gradually over ≥ 5 minutes, and/or ≥ 2 symptoms occur in succession (2) each individual aura symptom lasts 5-60 minutes (3) ≥ 1 aura symptom is unilateral (4) the aura is accompanied, or followed within 60 minutes, by headache	D. During headache ≥ 1 of the following: (1) nausea and/or vomiting (2) photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded	

The pathogenesis of migraine is not fully understood. In the past, it was considered a vascular disorder. A growing body of evidence suggests that vasodilation is neither necessary nor sufficient for provoking migraine attacks.⁽⁹⁻¹¹⁾ It is currently believed that migraine is a form of neurovascular headache. The nervous mechanisms stimulate cranial blood vessels, resulting in pain and further nerve activation. The trigeminovascular system plays a key role in the process. Its activation causes the release of various neuropeptides that promote the vascular and inflammatory changes associated with migraine pain. The pain signals are further transmitted through the brain stem to higher cortical pain centres. Moreover, central and

peripheral sensitisation induces a state of hyperexcitability in the cerebral cortex, leading to recurrent pain conditions and ultimately chronic migraine.^(9,10,12)

There are a wide range of nonpharmacologic and pharmacologic approaches available for the management of migraine. Acute therapies are used for rapidly relieving migraine attacks and restoring functional ability.⁽¹³⁾ On the other hand, daily preventive therapies may be needed to reduce the frequency, intensity and duration of migraine episodes.⁽¹⁴⁾ The current guideline from the European Federation of Neurological Societies (EFNS) recommends that preventive therapies should be considered for migraine patients when: (1) the quality of life, business duties, or school attendance are severely impaired; (2) frequency of attacks per month is two or higher; (3) migraine attacks do not respond to acute drug treatment; or (4) frequent, very long, or uncomfortable auras occur.⁽¹⁵⁾ It has been documented that nearly one-fourth of migraine patients were candidates for the treatment of preventive medications but the majority did not use them.⁽¹⁶⁾ In contrast, complementary and alternative medicine (CAM) has become increasingly popular among patients with headache disorders. The use of CAM is often driven by the concerns about the adverse effects and relatively high costs of preventive medications (**Table 2**). Some patients may opt for CAM after failing to respond to previous medication treatment.⁽¹⁷⁻¹⁹⁾ It is noteworthy that most migraineurs do not discuss the use of CAM with their physicians.^(20,21) Instead, they generally obtain CAM information through their relatives or acquaintances.⁽¹⁸⁾ Among different CAM modalities for the prophylaxis of migraine, nutraceuticals are readily available in pharmacies and health food stores. As the health professionals most accessible to the public, pharmacists should play an important role in providing evidence-based information about various nutraceuticals. Thus, the objective of this review is to summarise the current body of literature describing the efficacy of seven widely available nutraceuticals for migraine prevention in adults.

Table 2. First-line preventive medications recommended by American Academy of Neurology (AAN) and European Federation of Neurological Societies (EFNS)		
Class	Medication	Main adverse effects ⁽²²⁻²⁴⁾
Beta-blockers	Propranolol ^{a,b} Metoprolol ^{a,b} Timolol ^a	Fatigue, exercise intolerance
Antiepileptic drugs	Valproic acid and its derivatives ^{a,b} Topiramate ^{a,b}	Liver toxicity, drowsiness, nausea, weight gain, tremor, teratogenicity Paresthesia, weight loss, fatigue, nausea
Calcium channel blockers	Flunarizine ^b	Drowsiness

^a Level A recommendation based on AAN guideline⁽²³⁾

^b Level A recommendation based on EFNS guideline⁽¹⁵⁾

FEVERFEW

Feverfew (*Tanacetum parthenium*) is a perennial plant in the Asteraceae family (**Figure 1**). It has been used for different indications including fever, dysmenorrhoea, insect bites, arthritis, and other inflammatory conditions for centuries.^(6,25,26)

Chemically, feverfew contains various sesquiterpene lactones, flavonoids, and volatile oils. Parthenolide, which can be derived from the superficial leaf glands of the plant, is believed to be the major active constituent responsible for its properties.⁽²⁶⁾ Feverfew is likely to exert its anti-migraine actions through several mechanisms. In vitro data have shown that feverfew reduces serotonin secretion from platelets and leukocytes. It also inhibits prostaglandin synthesis and vascular smooth muscle spasm, which are involved in the pathogenesis of migraine.⁽²⁶⁻³¹⁾



Figure 1. A flower of feverfew (*Tanacetum parthenium*) (Left) and a diagram of the whole plant (right).

Multiple randomised placebo-controlled trials have been conducted to evaluate the role of feverfew in the prophylaxis of migraine. Nonetheless, these studies yielded conflicting results and were limited by small sample size and methodological flaws. The results of the clinical studies are summarised in **Table 3**. Certain formulations of feverfew seem to have promising benefits. In two studies conducted in the 1980s, the prophylactic treatment of dried, powdered feverfew leaves showed positive clinical results. One parallel-group study included 17 migraineurs who had been self-treated with raw feverfew leaves for more than three years before the study entry. While the patients who continued to take powdered feverfew leaves (50 mg daily) did not experience any differences from baseline, those in the placebo group reported significantly more migraine episodes after stopping their previous feverfew treatment.⁽³²⁾ However, the frequency of attacks did not differ significantly between the two groups.⁽³³⁾ In another double-blind crossover study with a larger sample size (n=59), a 24% reduction in the frequency of migraine episodes was observed in those receiving dried feverfew leaves (82 mg daily) for a month.⁽³⁴⁾ In addition, both studies found that feverfew treatment resulted in a lower incidence of nausea and vomiting as opposed to placebo.^(32,34) Another formulation of feverfew showing favourable effects is a carbon dioxide (CO₂) extract enriched with parthenolide. In a multicentre, dose-response trial with a parallel-group design (n=147), three different dosage regimens of this special extract were compared with placebo. Following 12 weeks of treatment, none of the dosage regimens showed significant benefits for migraine prophylaxis in the intention-to-treat analysis. Further analysis revealed that one of the dosage regimens (6.25 mg three times daily) markedly decreased the number

of migraine attacks in a subgroup of patients with more than four episodes monthly at baseline.⁽³⁵⁾ The positive finding of this subgroup analysis was later confirmed by a larger multicentre trial (n=170). The beneficial effects started after one month of treatment and lasted for at least four months.⁽³⁶⁾ On the contrary, a dried alcoholic extract of feverfew failed to demonstrate any benefits over placebo for preventing migraine. This feverfew extract was standardised to contain 0.5 mg of parthenolide after extensive processing and was taken daily by 44 migraineurs in the placebo-controlled crossover study.⁽³⁷⁾ The contradictory results associated with different formulations imply that the anti-migraine effects of feverfew leaves may be attributable to some unknown constituents in addition to parthenolide.^(37,38)

In the clinical trials, the most documented adverse events were mild gastrointestinal complaints including abdominal pain, nausea, diarrhoea, flatulence, and constipation.^(32,34-37) Mouth ulceration was also reported in the two trials using dried feverfew leaves.^(32,34) It has been speculated that this issue is a contact phenomenon and can be minimised by encapsulating the feverfew leaves.^(32,36,39) Moreover, a 'post-feverfew syndrome' has been observed in some of the patients who discontinued long-term feverfew treatment and switched to placebo. The withdrawal symptoms included nervousness, tension headache, insomnia, fatigue, and joint pain or stiffness.⁽³²⁾ Due to its potential antiplatelet activity, feverfew should be used cautiously with blood-thinning medications such as warfarin and aspirin.⁽²⁶⁾ Pregnant women should avoid feverfew because it may stimulate uterine contraction.^(19,26)

BUTTERBUR

Butterbur (*Petasites hybridus*), as shown in **Figure 2**, is a perennial shrub that also belongs to the Asteraceae family. It has traditionally been used for the treatment of asthma, cough,

and urogenital tract spasms. The major active constituents are two sesquiterpenes called petasin and isopetasin.^(40,41) While petasin can inhibit the lipoxygenase pathway and leukotriene production, isopetasin can increase prostaglandin metabolism. Some other constituents of butterbur may also have inhibitory effects on cyclooxygenase-2 (COX-2). Additionally, petasin and its analogues, which have a high affinity for cerebral blood vessels, may act as calcium channel blockers in smooth muscle cells and enhance vascular wall relaxation.⁽⁴⁰⁻⁴²⁾ The anti-inflammatory, anti-spasmodic, and calcium channel blocking effects of butterbur provide good rationales for its use in the prophylaxis of migraine.



Figure 2. Photo of a flowering butterbur plant (*Petasites hybridus*) (Left) and its drawing diagram (Right).

Based on the current American and European guidelines for migraine management, the efficacy of butterbur is supported by the highest level of evidence among all nutraceuticals.^(15,43) In fact, only two randomised clinical trials have been conducted to investigate the anti-migraine effects of butterbur in adult patients. Both studies used a patented CO₂-extract of butterbur standardised to contain a minimum of 15% of petasin and its analogues.⁽⁴²⁾ In the first study, 60 migraine patients were randomised to receive either butterbur (50 mg twice daily) or placebo for a period of 12 weeks, with 58

Table 3. Randomised controlled trials of feverfew for migraine prophylaxis

Study	Design	N	Treatment	Length of treatment (months)	Results (primary outcomes)
Johnson et al. (1985) ⁽³²⁾	Two parallel groups Double-blind	17	50 mg of powdered feverfew leaves daily vs placebo (All patients treated with raw feverfew leaves at baseline)	6	↑ headache frequency from baseline in placebo group (mean number of attacks monthly: 1.22±0.54 with feverfew at baseline, 3.43±1.02 with placebo; p<0.02) ↓ incidence of nausea and vomiting with feverfew (39 occasions with feverfew, 116 occasions with placebo; p<0.05)
Murphy et al. (1988) ⁽³⁴⁾	Crossover study Double-blind	59	82 mg of powdered feverfew leaves daily vs placebo	4	↓ headache frequency with feverfew (mean number of attacks: 3.6±0.2 with feverfew, 4.7±0.3 with placebo; p<0.005) ↓ incidence of nausea and vomiting with feverfew (49% with feverfew, 56% with placebo; p<0.02)
De Weerd et al. (1996) ⁽³⁷⁾	Crossover study Double-blind	44	Alcoholic extract of feverfew (standardised to 0.5 mg of parthenolide) vs placebo	4	No significant differences in frequency and severity of attacks between feverfew and placebo groups
Pfaffenrath et al. (2002) ⁽³⁵⁾	Four parallel groups Double-blind	147	Three different doses of CO ₂ -extract of feverfew (2.08 mg, 6.25 mg and 18.75 mg three times daily) vs placebo	3	↓ headache frequency with 6.25 mg of feverfew three times daily in a subgroup with > 4 episodes monthly at baseline (mean change in attacks: -1.8±1.5 with this dose, -0.3±1.9 with placebo)
Diener et al. (2005) ⁽³⁶⁾	Two parallel groups Double-blind	170	6.25 mg of CO ₂ -extract of feverfew three times daily vs placebo	4	↓ headache frequency with feverfew (mean change in attacks: -1.9±0.2 with feverfew, -1.3±0.2 with placebo; p=0.0456)

of them completing the study. According to the per-protocol analysis, the treatment of butterbur reduced the number of attacks per month by 45.5-60.6% from baseline, which was significantly better than placebo. Furthermore, marked improvements were observed with butterbur treatment in the intensity and duration of migraine after 8 weeks of treatment.⁽⁴⁴⁾ An independent reanalysis of the same study was published later, using an intention-to-treat approach. Like the original report, the reanalysis yielded positive results and added that the proportion of responders (with a 50% or greater reduction in migraine frequency from baseline) was much higher in the butterbur group (45%) than in the placebo group (15%).⁽⁴⁵⁾ In another three-arm, parallel-group trial completed by a total of 233 migraineurs, a higher dosage regimen of butterbur (75 mg twice daily) was superior to the lower dosage regimen (50 mg twice daily) and placebo in reducing the attack frequency. However, there were no significant differences between the lower dosage regimen of butterbur and placebo (Figure 3).⁽⁴⁶⁾

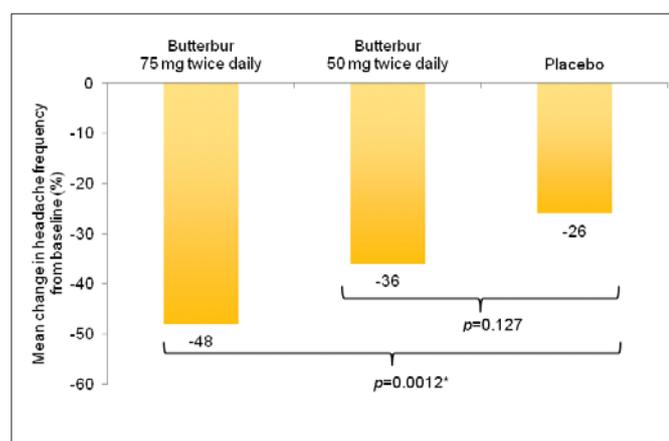


Figure 3. Clinical outcomes of different dosage regimens of butterbur for migraine prevention (N=233)⁽⁴⁶⁾

* Statistically significant

The CO₂-extract of butterbur was well tolerated in the clinical trials. Mild gastrointestinal upset, particularly burping, was the most commonly reported adverse events.^(41,42,46,47) Raw and unprocessed butterbur extracts contain pyrrolizidine alkaloids, which are hepatotoxic and carcinogenic. Nonetheless, the patented CO₂-extract of butterbur is practically free of these toxic constituents (< 0.088 ppm). Although rare cases of minor elevations of liver enzymes occurred in one clinical study, the changes were transient and considered clinically irrelevant by the investigators.⁽⁴⁵⁾ As there is a paucity of safety data, it is prudent for pregnant women to avoid taking butterbur for migraine prophylaxis.⁽⁴¹⁾

MAGNESIUM

As a major intracellular cation, magnesium is vital in a wide variety of physiological processes.⁽⁴⁸⁾ Magnesium deficiency may be involved in the pathogenesis of migraine. In comparison with healthy individuals, migraine patients have been found to have lower magnesium levels in their serum, saliva, and erythrocytes between and/or during attacks.⁽⁴⁹⁻⁵¹⁾ A reduction of

magnesium levels in the brain has also been observed during migraine episodes, as measured using *in vivo* ³¹ phosphorus nuclear magnetic resonance (NMR) spectroscopy.⁽⁵²⁾ Magnesium deficiency can also increase the sensitivity of N-methyl-D-aspartate (NMDA) receptors, which are linked to pain transmission within the nervous system, cerebral blood flow regulation, as well as cortical spreading depression (an underlying cause of aura).^(48,53-56) In addition, low magnesium levels can potentiate the contractile responses of blood vessels to serotonin, which is an important vasoconstrictor secreted by platelets during migraine attacks.^(48,57,58)

The results of clinical trials of magnesium for migraine prevention have been inconsistent. Peikert et al evaluated the efficacy of trimagnesium dicitrate (600 mg or 24 mmol magnesium daily) in the form of granular powders in a multicentre, double-blind, placebo-controlled study (n=81). At the end of the 12-week treatment, the number of migraine episodes per month was reduced by 41.6% and 15.8% in the magnesium group and the placebo group, respectively. The patients treated with magnesium had fewer headache days and used fewer doses of acute therapies compared with those receiving placebo. No significant differences were identified with respect to the intensity and duration of migraine attacks.⁽⁵⁹⁾ In another study involving 40 patients who suffered from migraine without aura, the prophylactic treatment of magnesium citrate (300 mg or 12 mmol magnesium twice daily) was superior to placebo in decreasing the frequency and severity of attacks.⁽⁶⁰⁾ More recently, magnesium oxide (500 mg daily) was compared with L-carnitine, the combination of magnesium and L-carnitine, as well as placebo in a single-blind study (n=133). The results also favoured magnesium supplementation over placebo.⁽⁶¹⁾ Moreover, in a study conducted by Facchinetti et al, a total of 20 women with menstrual migraine were randomly assigned to receive magnesium pyrrolidone carboxylic acid (360 mg magnesium daily) or placebo from the 15th day of the cycle to the next menses. A marked reduction in the number of days with migraine and total pain index was observed in the magnesium group.⁽⁶²⁾ However, there is a multicentre placebo-controlled trial (n=69) showing conflicting results.⁽⁶³⁾ The negative findings were possibly due to poor absorption of the magnesium salt (magnesium-L-aspartate-hydrochloride-trihydrate, 20 mmol magnesium daily) used in the study, as suggested by the high incidence (45.7%) of diarrhoea in the treatment group.^(48,63) The results of the randomised controlled trials are summarised in **Table 4**.

Patients should be advised that the prophylactic treatment of high-dose magnesium is likely to cause diarrhoea, which was complained by at least 10% of patients in the studies using the other magnesium salts. Nonetheless, most cases were mild and very few of them led to patient withdrawal.^(59,60) In overall, the vast majority of migraine patients can tolerate magnesium well.⁽⁶³⁾ Furthermore, magnesium supplementation should be used with caution in patients with renal diseases because they are at higher risk for toxicity. According to the current EFNS guideline, oral magnesium is the only nutraceutical recommended for migraine prophylaxis during pregnancy.⁽¹⁵⁾

Table 4. Randomised controlled trials of magnesium (Mg) for migraine prophylaxis

Study	Design	N	Treatment	Length of treatment (months)	Results (primary outcomes)
Facchinetti et al. (1991) ⁽⁶²⁾	Two parallel groups Double-blind Menstrual migraine only	20	Mg pyrrolidone carboxylic acid (360 mg Mg) daily vs placebo	2	↓ Pain Total Index with Mg ($p<0.03$)
Peikert et al. (1996) ⁽⁵⁹⁾	Two parallel groups Double-blind	81	Trimagnesium dicitrate (24 mmol Mg) daily vs placebo	3	↓ headache frequency with Mg (41.6% reduction from baseline with Mg, 15.8% reduction with placebo; $p<0.05$)
Pfaffenrath et al. (1996) ⁽⁶³⁾	Two parallel groups Double-blind	69	MAH (20 mmol Mg) daily vs placebo	3	No significant difference in % responders ^a between MAH and placebo groups (28.6% with Mg, 29.4% with placebo)
Koseoglu et al. (2008) ⁽⁶⁰⁾	Two parallel groups Double-blind	40	Mg citrate (12 mmol Mg) twice daily vs placebo	3	↓ headache frequency with Mg (post/ pretreatment ratios: 0.55 with Mg, 1.0 with placebo; $p=0.005$) ↓ severity with Mg (post/ pretreatment ratios: 0.57 with Mg, 1.0 with placebo; $p<0.001$)
Tarighat Esfanjani et al. (2012) ⁽⁶¹⁾	Four parallel groups Single-blind	133	500 mg/d Mg oxide, 500 mg/d L-carnitine, and 500 mg/d Mg oxide plus 500 mg/d L-carnitine vs placebo	3	↓ headache frequency with Mg oxide as compared with placebo ($p<0.006$) No significant differences in migraine days and severity between the four groups

^a Responders are defined as those with a 50% or greater reduction in intensity or duration of migraine attacks.
MAH: Magnesium-L-aspartate-hydrochloride-trihydrate

RIBOFLAVIN

Riboflavin, or vitamin B2, is essential for normal cellular growth, enzyme function, and energy production. In the mitochondria, riboflavin is converted into its two active coenzyme forms, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). Both FMN and FAD function as prosthetic groups in many enzyme systems and as catalysts of oxidation-reduction reactions, thereby playing a role in the electron transport chain of the Krebs cycle and other metabolic pathways.⁽⁶⁴⁾ Previous literature has revealed a decrease in mitochondrial phosphorylation potential in the brain of migraineurs during headache-free periods.^(65,66) It has been hypothesized that riboflavin may overcome this defect by enhancing brain energy metabolism.⁽⁶⁷⁾ Additionally, high-dose riboflavin can alleviate migraine-like headache in patients with mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS).^(68,69)

There is insufficient clinical evidence supporting its regular use for migraine prevention. After finding positive results in an open-label pilot study,⁽⁷⁰⁾ Schoenen et al conducted a randomised placebo-controlled trial of riboflavin that included 55 patients predominantly suffering from migraine without aura. The patients treated with riboflavin (400 mg daily) for three months reported marked improvements in the frequency of attacks and migraine days, as compared with those in the placebo group. The number needed to treat (NNT) to achieve at least 50% decrease in headache days was 2.3 (**Figure 4**).⁽⁷¹⁾ The benefits of riboflavin were also reported in two other studies of lower methodological quality. In an uncontrolled study, 23 patients were prescribed riboflavin (400 mg daily) for migraine prophylaxis. The number of attacks and the use of acute therapies were significantly reduced after three months of treatment. Conversely, the intensity and duration of attacks were

not affected.⁽⁷²⁾ Sandor et al demonstrated that riboflavin (400 mg daily) might be as efficacious as beta-blockers (metoprolol 200 mg or bisoprolol 10 mg daily) in the prophylaxis of migraine attacks although the study was limited by small sample size ($n=26$) and the absence of a placebo group.⁽⁷³⁾ Interestingly, according to a pharmacogenetic study, riboflavin showed higher efficacy in migraineurs with non-H mitochondrial DNA (mtDNA) haplotypes. The authors suggested that the result might have ethnic implications because mtDNA haplogroup H was primarily found in the European population.⁽⁷⁴⁾

The preventive treatment of riboflavin for migraine is generally safe. Rare cases of diarrhoea, abdominal pain, polyuria, and facial erythema occurred in the clinical studies but none of them were serious.^(71,72) Treatment adherence is particularly important because it takes approximately three months to reach the maximal effects of riboflavin.⁽⁷¹⁾

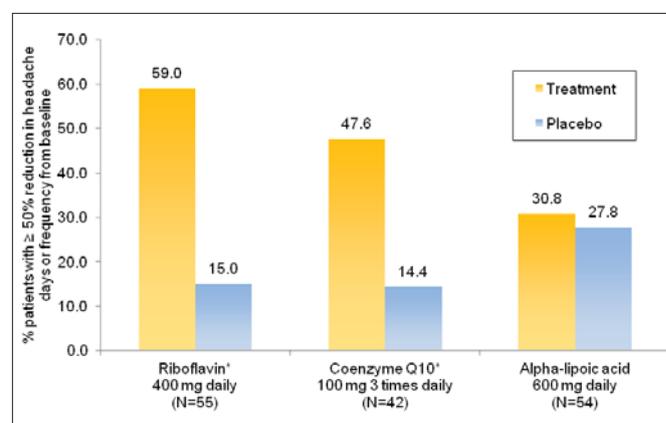


Figure 4. Proportion of responders in the randomised controlled trials of riboflavin (headache days),⁽⁷¹⁾ coenzyme Q10⁽⁷⁶⁾ and alpha-lipoic acid (headache frequency)⁽⁸⁰⁾

* Statistically significant ($p<0.05$)

OTHER NUTRACEUTICALS

Coenzyme Q10

Coenzyme Q10 is a key substance involved in the mitochondrial electron transport chain. Similar to riboflavin, coenzyme Q10 supplementation has been proposed to enhance mitochondrial oxidative phosphorylation and thus may have anti-migraine properties.⁽⁷⁵⁾ Two relevant clinical trials involving small numbers of patients have been carried out. Based on an uncontrolled trial (n=31), a three-month course of coenzyme Q10 (150 mg daily) treatment markedly reduced the number of headache days and the frequency of migraine episodes. However, it did not alleviate the intensity of migraine attacks.⁽⁷⁵⁾ The promising results were in line with those described in another randomised double-blind study. A higher dosage regimen (100 mg three times daily) of coenzyme Q10 was much better than placebo with respect to decreasing attack frequency, headache days, and days with nausea. The NNT to achieve a 50% or greater reduction in headache frequency was 3.0 (**Figure 4**). Coenzyme Q10 has a good safety profile, with few adverse events such as gastrointestinal upset and cutaneous allergy documented in the clinical trials.⁽⁷⁶⁾

Alpha-lipoic acid

Alpha-lipoic acid, also referred to as thioctic acid, can augment mitochondrial oxygen metabolism and energy production like riboflavin and coenzyme Q10.^(19,77) According to case studies, the treatment of alpha-lipoic acid can cause clinical and biochemical improvements in patients with mitochondrial cytopathies,^(78,79) whereas the findings of clinical trials are far from convincing. Encouraged by the positive results of a small open-label pilot study, Magis et al further examined the efficacy of alpha-lipoic acid (600 mg daily) in a multicentre, double-blind, placebo-controlled trial. Even though the within-group analysis revealed a significant reduction in headache frequency, headache days and severity, alpha-lipoic acid was not superior to placebo in all of these outcome variables (**Figure 4**). No adverse events were identified during the three-month treatment. The authors also acknowledged that the study was underpowered because the time limit for quality guarantee by the manufacturer was exceeded prior to the completion of patient recruitment.⁽⁸⁰⁾ More controlled trials are warranted to justify the use of alpha-lipoic acid for migraine prophylaxis.

Melatonin

Melatonin is an endogenous hormone that helps regulate circadian rhythms.⁽⁸¹⁾ It has been evidenced that migraineurs may have lower urinary concentrations of melatonin and its major metabolite compared with healthy individuals, indicating a potential relationship between migraine and melatonin secretion.^(82,83) Melatonin regulates neurovascular functions and modulates serotonin. It also protects against glutamate neurotoxicity and inhibits the release of dopamine. Its anti-inflammatory and anti-oxidant activities may also contribute to its anti-migraine effects.^(84,85) The clinical studies of melatonin yielded mixed findings. Peres et al conducted an open-label trial and found that the frequency, intensity and duration of migraine were significantly reduced among 32 migraineurs taking melatonin (3 mg 30 minutes before bedtime) for a month.⁽⁸⁶⁾ On the contrary, the treatment of extended-release melatonin (2 mg one hour before bedtime) did not show any benefits in a placebo-controlled crossover study (n=46).⁽⁸⁷⁾ Melatonin may potentially be a safe option for migraine prevention but its efficacy remains to be elucidated.⁽⁸⁸⁾

CONCLUSION

Migraine is one of the most disabling disorders that have substantial impact on patients' quality of life. According to the current guideline, preventive therapies are recommended for certain patients to reduce the frequency and severity of migraine episodes. In spite of the availability of effective prophylactic medications, many patients with migraine prefer nutraceuticals because they are often safer and less expensive. This review demonstrates that the clinical efficacy of various nutraceuticals for this indication is still controversial (**Table 5**). Based on two well-designed studies, butterbur appears to be an efficacious and well-tolerated option for preventing migraine. Magnesium and feverfew show promising benefits with reasonable safety profiles but the evidence is inconsistent. Riboflavin, coenzyme Q10 and alpha-lipoic acid can enhance mitochondrial function and thus may have a role in migraine prevention. However, most clinical trials of the three nutraceuticals are limited by small sample size and suboptimal methodological quality. Similarly, the anti-migraine effects of melatonin remain largely underexplored. In addition, there is currently a lack of studies comparing the efficacy of preventive

Table 5. Summary of clinical evidence and safety of selected nutraceuticals for migraine prophylaxis

Nutraceutical	Clinical evidence	Potential adverse effects
Feverfew (<i>Tanacetum parthenium</i>) ^(32,34-37)	Dried leaves may be efficacious. CO ₂ -extract may be beneficial for patients with a higher frequency of migraine attacks. More data are needed.	Abdominal pain, nausea, diarrhoea, flatulence, constipation, post-feverfew syndrome, and mouth ulceration
Butterbur (<i>Petasites hybridus</i>) ⁽⁴⁴⁻⁴⁶⁾	Efficacy is supported by two clinical trials of high methodological quality.	Gastrointestinal upset, burping
Magnesium ⁽⁵⁹⁻⁶³⁾	Certain magnesium salts may be beneficial. More data are needed.	Diarrhoea
Riboflavin (Vitamin B2) ⁽⁷⁰⁻⁷³⁾	Limited data.	Diarrhoea, abdominal pain, polyuria, and facial erythema
Coenzyme Q10 ^(75,76)	Limited data.	Gastrointestinal upset and cutaneous allergy
Alpha-lipoic acid (Thioctic acid) ⁽⁸⁰⁾	Inconclusive evidence.	None reported
Melatonin ^(86,87)	Mixed evidence. Efficacy may be dose-dependent.	None reported

medications and nutraceuticals. More well-designed clinical trials are necessary to confirm the beneficial effects and long-term safety of these nutraceuticals in the prophylaxis of migraine.

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Author's background

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The Annual General Meeting and 65th Anniversary Dinner of the Pharmaceutical Society of Hong Kong

The Annual General Meeting of the Pharmaceutical Society of Hong Kong was held on 6 December 2014 at 5:00p.m at the Pearl Ballroom, 2/F, Eaton Hotel, 380 Nathan Road, Kowloon, Hong Kong. The President, Ms. Mary Cheng reported on the progress and activities for 2014 and the Treasurer, Ms. Candy Tai reported on the financial standing of PSHK. The election of GC members began at around 5:40p.m. Last year's President and the three Pharmacy & Poisons Board Representatives naturally become GC members for 2015. There were 13 pharmacists nominated as General Council members and 11 were elected. Mrs. Mary Cheng after serving for 3 years as president step down and Mr. Philip Chiu, Senior Pharmacist at Mannings, was elected as the new president of PSHK. The meeting was followed by the AGM of the Joint Pharmaceutical Services Foundation (JPSF) and the motion of adopting the newly elected GCs of PSHK as the members of the GC of this Foundation and the Treasurer Report of JPSF were adopted in the AGM.

After the AGM, as a special commemorative event for the 65th Anniversary of PSHK, there was a seminar on the topic: "Stroke Prevention in AF patients: Warfarin, Aspirin or NOACs?" delivered by Prof. Tse Hung Fat (Deputy Director, Research Center of the Heart, Brain, Hormone and Healthy Aging, LKS Faculty of Medicine, HKU). Prof. Tse was an

excellent speaker and he discussed with the audience the new oral anticoagulants and revealed the higher occurrence of AF in Hong Kong patients.

After the seminar, Mrs, Mary Cheng presented the special awards to two pharmacists: Mr. Johnny Wong and Mr. Peter Leung. Mr. Johnny Wong was given a commendation for active participation and contribution to the Drug in Sports database revamp and the e-Drug Apps project. Mr. Peter Leung was given a commendation for active participation, hard work and dedication in carrying out his duties as Vice President.

The 65th Anniversary Dinner was held immediately after the award presentation. The participants enjoyed the delicious Chinese cuisine and the opportunity to chat with old and new friends. Each participant was given a commemorative stainless steel hot water bottle with PSHK embossed on it. There were also table prizes and lucky draw for all participants.



Prof. TSE Hung Fat delivered a talk on new oral anticoagulants.



Mrs. Mary Cheng presented the award of appreciation to Mr. Johnny Wong



Mrs. Mary Cheng presented the award of appreciation to Mr. Peter Leung



Group photo of some past and current GCs of the Pharmaceutical Society of Hong Kong

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*Newly elected GC members (They replaced Phoebe Chan and Eric Yau)



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(Part I) Personal Particulars

# Title: Prof. <input type="checkbox"/> Dr. <input type="checkbox"/> Mr. <input type="checkbox"/> Ms. <input type="checkbox"/> Mrs. <input type="checkbox"/>	# Last Name: _____	# First Name: _____
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Working Sector: <input type="checkbox"/> Community <input type="checkbox"/> Education <input type="checkbox"/> Government <input type="checkbox"/> Hospital <input type="checkbox"/> Industry <input type="checkbox"/> Student <input type="checkbox"/> Others		
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<input type="checkbox"/> The Pharmaceutical Society of Hong Kong (PSHK)	Membership No.: _____	
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Mandatory fields

(Part II) Registration Fee

Category		Early-Bird* (On or Before 16 Feb 2015)	Standard Fee (17 Feb 2015 – 20 Mar 2015)
Full	Member (PSHK / SHPHK / PPA)	<input type="checkbox"/> HK\$ 1,100	<input type="checkbox"/> HK\$ 1,300
	Non-member	<input type="checkbox"/> HK\$ 1,300	<input type="checkbox"/> HK\$ 1,500
Partial Registration	Day 1 lectures only	<input type="checkbox"/> HK\$ 600	<input type="checkbox"/> HK\$ 600
	Day 2 lectures only (includes Day 2 lunch symposium)	<input type="checkbox"/> HK\$ 800	<input type="checkbox"/> HK\$ 800
	Day 1 and Day 2 lectures only (includes Day 2 lunch symposium)	<input type="checkbox"/> HK\$ 850	<input type="checkbox"/> HK\$ 1,050
	Conference dinner only	<input type="checkbox"/> HK\$ 1,000	<input type="checkbox"/> HK\$ 1,000
Special Offer [†]	Day 1 and Day 2 lectures only (includes Day 2 lunch symposium)	<input type="checkbox"/> HK\$ 500 Affiliation (please indicate): _____	

For postal registration payment, foreign cheque is not accepted.

I have enclosed a Bank Draft / Cheque No. _____ of HK\$ _____ made payable to "The Pharmaceutical Society of Hong Kong Ltd".

Please send the completed registration form and the payment to "Conference Secretariat of Hong Kong Pharmacy Conference, MIMS (Hong Kong) Ltd., 27/F., OTB Building, 160 Gloucester Road, Wanchai, Hong Kong".

* To receive the early-bird discount, the registration form received must be postmarked before **16 February 2015**.

† Only for LOCAL registrants who are undergraduates majoring in Pharmacy, Medicine, Nursing or Chinese Medicine; students of Higher Diploma in Pharmaceutical Technology (IVE); pharmacy interns; members of the Pharmaceutical Staff Association (PSA); members of the Hong Kong Pharmacy Technicians Association (HKPTA) or members of the Hong Kong Society of Pharmaceutical Technology and Health Care Professionals (PTHcP). **Relevant affiliations must be stated above to be eligible to apply for the special offer.** In case of any disputes, the decision of the Conference Organizing Committee shall be final.



HONG KONG PHARMACY CONFERENCE 2015 28 – 29 MARCH 2015

Registration Information

Confirmation of Registration

Successful registrants by postal registration will receive a confirmation letter by post approximately two weeks before the conference while registrants by online registration will receive a confirmation e-mail. If the registration form and payment are received **after 20 March 2015**, the confirmation will only be available for collection on-site.

Conference Venue

The conference will be held at the Meeting Rooms S221-S230, Level 2, Phase 1 (Old Wing), Hong Kong Convention and Exhibition Centre, 1 Expo Drive, Wanchai, Hong Kong.

Continuing Education Units (CEU)

The conference is an approved non-PCCC conference. One-day and two-day attendees are eligible to receive 6 and 10 CEU respectively.

Cancellation of Registration

Any written cancellation notice should be sent to “Conference Secretariat of Hong Kong Pharmacy Conference, MIMS (Hong Kong) Ltd., 27/F., OTB Building, 160 Gloucester Road, Wanchai, Hong Kong”. Cancellations received in writing **before 19 January 2015** will qualify for a full refund. Cancellations thereafter are non-refundable. The Conference Organizing Committee reserves the right to process refunds after the conference concludes. **Registration is not transferable.**

Arrangement for Overseas Delegates by Telegraphic Transfer

Payment must be denominated in Hong Kong dollars. Please submit a copy of the telegraphic transfer receipt together with the registration form by e-mail to registration@pharmacyconference.org

Enquiries

For enquiries, please contact the Conference Secretariat by e-mail to registration@pharmacyconference.org or by phone to Ms. Agnes Ku on (852) 2155 8557.

JANUMET XR® (MSD)

Prepared by Lucilla Leung

Active Ingredient:

JANUMET XR tablets contain two oral antidiabetic medications used in the management of type 2 diabetes: sitagliptin and metformin hydrochloride extended-release.

Presentation:

Each tablet of 50mg/500mg contains SITAGLIPTIN 50 mg/ metformin HCL extended-release 500 mg

Each tablet 50mg/1000mg contains SITAGLIPTIN 50 mg/ metformin HCL extended-release 1000 mg

Each tablet 100mg/1000mg contains SITAGLIPTIN 100 mg/ metformin HCL extended-release 1000 mg

Pharmacological Properties:

JANUMET XR

JANUMET XR tablets combine two antidiabetic medications with complementary mechanisms of action to improve glycemic control in adults with type 2 diabetes: sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride extended-release, a member of the biguanide class.

Sitagliptin

Sitagliptin is a DPP-4 inhibitor, which exerts its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity *in vitro* at concentrations approximating those from therapeutic doses.

Metformin hydrochloride

Metformin is a biguanide that improves glycemic control in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in either patients with type 2 diabetes or healthy subjects except in certain circumstances [see *Warnings and Precautions (5.9)*] and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Indications:

JANUMET XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin extended-release is appropriate.

Important Limitations of Use

JANUMET XR should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. JANUMET XR has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUMET XR.

Dosage and Administration:

The dose of JANUMET XR should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin. Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider.

- In patients not currently treated with metformin, the recommended total daily starting dose of JANUMET XR is 100 mg sitagliptin and 1000 mg metformin hydrochloride (HCl) extended-release. Patients with inadequate glycemic control on this dose of metformin can be titrated gradually, to reduce gastrointestinal side effects associated with metformin, up to the maximum recommended daily dose.
- In patients already treated with metformin, the recommended total daily starting dose of JANUMET XR is 100 mg sitagliptin and the previously prescribed dose of metformin.
- For patients taking metformin immediate-release 850 mg twice daily or 1000 mg twice daily, the recommended starting dose of JANUMET XR is two 50 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablets taken together once daily.
- Maintain the same total daily dose of sitagliptin and metformin when changing between JANUMET (sitagliptin and metformin HCl immediate-release) and JANUMET XR. Patients with inadequate glycemic control on this dose of metformin can be titrated gradually, to reduce gastrointestinal side effects associated with metformin, up to the maximum recommended daily dose.

JANUMET XR should be administered with food to reduce the gastrointestinal side effects associated with the metformin component. JANUMET XR should be given once daily with a meal preferably in the evening. JANUMET XR should be swallowed whole. The tablets must not be split, crushed, or chewed before swallowing.

The 100 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablet should be taken as a single tablet once daily. Patients using two JANUMET XR tablets (such as two 50 mg sitagliptin/500 mg metformin hydrochloride extended-release tablets or two 50 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablets) should take the two tablets together once daily.

Patients treated with an insulin secretagogue or insulin Co-administration of JANUMET XR with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

No studies have been performed specifically examining the safety and efficacy of JANUMET XR in patients previously treated with other oral antihyperglycemic agents and switched to JANUMET XR. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

Contraindications:

JANUMET XR is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels greater than or equal to 1.5 mg/dL for men, greater than or equal to 1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
- Hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to JANUMET XR or sitagliptin, such as anaphylaxis or angioedema.

Precautions:

Pancreatitis

There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin with or without metformin. After initiation of JANUMET XR, patients should be observed carefully for signs and symptoms of pancreatitis.

Impaired Hepatic Function

Since impaired hepatic function has been associated with some cases of lactic acidosis, JANUMET XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Drug Interactions:

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with JANUMET XR, as the risk of lactic acidosis may increase.

Cationic Drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal

tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of JANUMET XR and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

The Use of Metformin with Other Drugs

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving JANUMET XR the patient should be closely observed to maintain adequate glycemic control.

Assessment of Renal Function

Metformin and sitagliptin are substantially excreted by the kidney.

Metformin hydrochloride

The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, JANUMET XR is contraindicated in patients with renal impairment.

Before initiation of JANUMET XR and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated (e.g., elderly), renal function should be assessed more frequently and JANUMET XR discontinued if evidence of renal impairment is present.

Sitagliptin

There have been postmarketing reports of worsening renal function in patients taking sitagliptin with or without metformin, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with JANUMET XR and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and JANUMET XR discontinued if evidence of renal impairment is present.

Side Effects:

Table 1 summarizes the most common ($\geq 5\%$ of patients) adverse reactions reported (regardless of investigator assessment of causality) in a 24-week placebo-controlled factorial study in which sitagliptin and metformin immediate-release were co-administered to patients with type 2 diabetes inadequately controlled on diet and exercise.

Forensic Classification:

P1S1S3

Table 1: Sitagliptin and Metformin Immediate-Release Co-administered to Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in $\geq 5\%$ of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo)*				
	Number of Patients (%)			
	Placebo N = 176	Sitagliptin 100 mg once daily N = 179	Metformin Immediate-Release 500 mg or 1000 mg twice daily † N = 364†	Sitagliptin 50 mg twice daily + Metformin Immediate-Release 500 mg or 1000 mg twice daily † N = 372†
Diarrhea	7 (4.0)	5 (2.8)	28 (7.7)	28 (7.5)
Upper Respiratory Tract Infection	9 (5.1)	8 (4.5)	19 (5.2)	23 (6.2)
Headache	5 (2.8)	2 (1.1)	14 (3.8)	22 (5.9)

* Intent-to-treat population.

† Data pooled for the patients given the lower and higher doses of metformin.

OSENI
(Takeda)
Prepared by Ivy Chan

Active Ingredients:

Alogliptin and pioglitazone

Presentations:

Film-coated tablet 25mg+15mg

Film-coated tablet 25mg+30mg

Pharmacological Properties:

OSENI combines two antihyperglycaemic medications with complementary and distinct mechanisms of action to improve glycaemic control in patients with type 2 diabetes mellitus: alogliptin, a dipeptidyl-peptidase-4 (DPP-4) inhibitor, and pioglitazone, a member of the thiazolidinedione class. Studies in animal models of diabetes showed that concomitant treatment with alogliptin and pioglitazone produced both additive and synergistic improvements in glycaemic control, increased pancreatic insulin content and normalised pancreatic beta-cell distribution.

Indications:

OSENI is indicated to improve glycemic control in adult patients (≥ 18 years old) with type 2 diabetes mellitus (T2DM):

- as an adjunct to diet and exercise in patients inadequately controlled on pioglitazone or in patients already being treated with this combination of alogliptin and pioglitazone and for whom metformin is inappropriate due to contraindications or intolerance.
- in combination with metformin when diet and exercise plus dual therapy with pioglitazone and metformin do not provide adequate glycemic control.

Dosage & Administration:

For patients inadequately controlled on pioglitazone alone, the recommended dose of OSENI should provide alogliptin dosed at 25 mg once daily and pioglitazone at the daily dose (15 mg or 30 mg) already being taken.

For patients inadequately controlled on dual therapy with pioglitazone and metformin, the dose of metformin should be maintained, and OSENI administered concomitantly; alogliptin should be dosed at 25 mg once daily and pioglitazone at the daily dose (15 mg or 30 mg) already being taken.

For patients switching from separate tablets of alogliptin and pioglitazone, both alogliptin and pioglitazone should be dosed at the daily dose already being taken.

Contraindications:

OSENI is contraindicated in patients with:

- New York Heart Association (NYHA) Class I to IV cardiac status.
- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container.
- Severe hepatic impairment (Child-Pugh score > 9)
- Pregnancy. Oral antidiabetic agents should not be given
- Active bladder cancer or a history of bladder cancer.
- Uninvestigated macroscopic haematuria.
- Unstable and/or insulin-dependent (Type 1) diabetes mellitus.

Precautions:

Weight gain, fractures, congestive heart failure, acute coronary syndrome, edema, hypoglycemia, bladder cancer, change in hemoglobin values, hepatic impairment, increased liver enzymes, hepatocellular injury, pancreatitis, hypersensitivity reactions, decreased visual acuity, renal impairment or ESRD requiring dialysis, premenopausal anovulatory patient with insulin resistance, geriatric patient (>65 yr).

Drug Interactions:

Alogliptin: Atorvastatin, glyburide, fluconazole, gemfibrozil, ketoconazole, voglibose. Pioglitazone: Fexofenadine HCl, atorvastatin Ca.

Side Effects:

Influenza, nasopharyngitis, headache, nausea, sinusitis, upper respiratory tract infection, cough, rash, hypertension

Forensic Classification:

P1S1S3

Choose

EliquisTM
apixaban

NEW

The **first and only** anticoagulant to demonstrate similar safety profile to aspirin^{1,3} and superiority to warfarin^{1,2} in 3 key outcomes



To get **BOTH** safety and efficacy

ELIQUIS® (apixaban) 2.5 mg & 5 mg Film-coated Tablets Prescribing Information

INDICATION: Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA), age \geq 75 years, hypertension, diabetes mellitus or symptomatic heart failure (NYHA Class \geq II). **DOSE AND ADMINISTRATION:** Recommended usual dose - 5mg PO BID. Patients with \geq 2 of the following criteria: serum Cr \geq 1.5 mg/dL (133 μ mol/L), age \geq 80 years, or body weight \leq 60 kg, reduce dose to 2.5 mg PO BID. Please refer to full prescription insert for complete details on Dosage and Administration. Eliquis is not recommended in children and adolescents below the age of 18. **CONTRAINDICATIONS:** Eliquis is contraindicated in patients with hypersensitivity to apixaban or to any of the excipients listed in full prescription insert, clinically significant active bleeding, hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Please refer to full prescription insert for complete Contraindications list. **SPECIAL WARNINGS AND PRECAUTIONS:** Please refer to full prescription insert for complete Special Warnings and Precautions. **Haemorrhage risk:** Carefully observe for signs of bleeding. Use with caution in conditions with increased risk of haemorrhage. Discontinue administration if severe haemorrhage occurs. **Renal impairment:** No dose adjustment in mild or moderate renal impairment. Reduce dose to 2.5mg PO BID in Patients with severe renal impairment (CrCl 15 – 29 mL/min). Not recommended in patients with creatinine clearance $<$ 15 mL/min or in patients undergoing dialysis. **Elderly Patients:** The co-administration of Eliquis with acetylsalicylic acid in elderly patients should be used cautiously because of a potentially higher bleeding risk. **Hepatic impairment:** Not recommended in severe hepatic impairment. Perform liver function testing before starting Eliquis. **Surgery and invasive procedures:** Discontinue at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding or interventions for which the risk of bleeding would be unacceptable. Discontinue at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled. If surgery or invasive procedures cannot be delayed, exercise appropriate caution and weigh bleeding risk against the urgency of intervention. Please see full prescription insert for details. **Laboratory parameters:** Clotting tests (PT, INR, and aPTT) are not recommended to assess the pharmacodynamic effects of Eliquis. **DRUG INTERACTIONS:** Consult full prescription insert for full details on interactions. **PREGNANCY AND LACTATION:** Not recommended during pregnancy. Discontinue breastfeeding or discontinue Eliquis therapy. **UNDESIRABLE EFFECTS:** Please refer to full prescription insert for complete list. **Common:** Eye haemorrhage (including conjunctival haemorrhage), haematoma, epistaxis, gastrointestinal haemorrhage (including haematemesis and melena), rectal haemorrhage, gingival bleeding, haematuria, contusion. **Uncommon:** hypersensitivity (including skin rash, anaphylactic reaction and allergic oedema), brain haemorrhage, other intracranial or intraspinal haemorrhage (including subdural haematoma, subarachnoid haemorrhage, and spinal haematoma), intra-abdominal haemorrhage, haemorrhoidal haemorrhage, haematochezia, mouth haemorrhage, abnormal vaginal haemorrhage, urogenital haemorrhage, application site bleeding, occult blood positive, traumatic haemorrhage, post procedural haemorrhage, incision site haemorrhage. **Rare:** Respiratory tract haemorrhage (including pulmonary alveolar haemorrhage, laryngeal haemorrhage and pharyngeal haemorrhage), retroperitoneal haemorrhage. Adverse events should be reported. Adverse events should also be reported to Bristol-Myers Squibb Pharmaceuticals Ltd Medical Information on medinfo.hongkong@bms.com directly or via phone at the following toll free number for HK 3002 7890 and for Macau 0800348

Consult full prescription insert prior to prescribing.

References: 1. Data on file, Bristol-Myers Squibb. 2. Granger CB, Alexander JH, McMurray JJ, et al; for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):961–992. 3. Connolly SJ, Ezekowitz J, Joyner C, et al; for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364(9):806–817.



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