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Editorial

It is sad to learn that Mr. Michael Leung, our Managing Editor, will leave *The Hong Kong Pharmaceutical Journal (HKPJ)* on personal grounds. Michael's editorship of the *HKPJ* over the past few years had been outstanding. During his editorship, Michael had successfully embraced the information technology revolution as it had affected periodicals. He had not only expanded the content of the *HKPJ* but had launched a remarkable number of highly successful new "niche" publications under the *HKPJ* banner. Let us congratulate Michael upon his release from the unrelenting treadmill of quarterly journalism and wish him every happiness in his new found freedom, and express the hope that he will enjoy a long and happy and fulfilling future. It is a privilege for me to play my part in leading the *HKPJ* forward, and I must take this opportunity to pay tribute to my colleagues, both from the *HKPJ* and across the wider membership, for their sincere and wholehearted engagement with the *HKPJ*.

This has been a year in which the three professional pharmacy bodies and other pharmacist groups have made great progress towards the goal of upgrading the image of pharmacists. To name a few of those events that the pharmacy bodies and pharmacist groups participate: the 4P Drug Compliance and Counseling Services (DCCS) program, the smoking cessation program, the implementation of the Hospital Authority Drug Formulary, the dispensing of "Self Financed Items" in the community, the Protection Surveillance System to monitor the possible outbreak of infectious disease in the community in collaboration with the Centre for Health Protection of the Department of Health, the Legco Health Panel discussion on the Separation of Prescribing from Dispensing Drugs (SPD), Welfare and Food Bureau's public consultation on the discussion paper "Building a Healthy Tomorrow" in the formulation of the future health care delivery model and the healthcare financing system in Hong Kong, etc.. We are in fact in such a harmony and union that has never happened before. We should set aside past differences in a spirit of fellowship and compromise. The time has come for everyone to pull together for the sake of the profession and for the sake of how the wider world perceives it.

With much work still to do to ensure that our profession has the framework it needs for the future, we can however look back on 2005 as a year when solid foundations were laid for the years to come. Let us continue our united effort and strive to integrate into the health care team and playing an equally important, yet complementary role to that of doctors, nurses and other health care professionals to bring about better health gains for the public and to advance our profession.

The *HKPJ* also wishes to invite papers and articles from all sectors of pharmacy. With your continual support, the *HKPJ* will become a valuable asset of our profession. Our editorial and business staff will strive to upkeep the quality of the *HKPJ* and hope that one day our *HKPJ* will become a renowned journal receiving a citation impact from the other scientific journals.

Warren Tsang
Managing Editor

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Editorial

Pharmacy Practice

Drug & Therapeutics

Phamaceutical Technology

Herbal Medicines & Nutraceuticals

Society Activities

New Products

Should Generic Drugs be Used in Hong Kong?

Wong, Helen

I INTRODUCTION

When a drug is developed and introduced to the market for the first time, the medicinal product is typically called as an innovator's product or branded product. After a period of time, another company produces a medicinal product in which the active ingredient(s) is (are) the same as the innovator's product and bring it to the market for competition with the original brand. This later developed product is termed as a "generic" product. Generic drugs have no medical advantage over the innovators' drugs, but they are cheaper. Theoretically, generic drugs should at least produce similar therapeutic effects as what innovators' drugs do.

Although generic drugs are offered at much lower prices than the originals, their use is disputable. The discussion on whether generic drugs should be used and the extent of their use has been vigorous. This topic today is not only discussed worldwide but also in the Asian region and the local society. There are several concerns which include the safety and quality of generic drugs, a country's financial burden and health status, the possible impact to drug research and development, and subsequently the long-term human health.

In the following sections, the above-mentioned concerns on use of generic drugs will be studied. The international recommendations and practices will firstly be introduced. Then a closer look to Hong Kong (HK) environment will be taken and the topical question, "*Should generic drugs be used in Hong Kong?*" will be discussed.

II WORLDWIDE RECOMMENDATIONS AND PRACTICES

i) Value of generic drugs

Generic drugs carry an important function in public health. Since they are sold at much lower prices than the innovators' drugs, using generic drugs can lower the overall national healthcare costs. This is particularly crucial to less developed and poor nations, which cannot afford the minimum pharmaceutical needs for their citizens. Generic drugs help to solve the issue of access to medicines. Until now, many people in Africa and Asia are still suffering or even die from lack of pharmaceutical care. In more developed nations, a lowering in the overall healthcare cost allows nations to have extra funding in improving their health services or else where.

The World Health Organization (WHO) emphasizes lack of access to essential medicines (Table 1) as one of the most serious global public health problems. 316 essential medicines (active substances) are listed in the WHO Model List of essential medicines [1]. About 30% of the world's population lacks regular access to essential medicines and the figures rise to over 50% in the poorest parts of Africa and Asia [2]. In many low-and middle-income countries, health sector reforms have led to insufficient public funding for health [2]. Generic versions of essential medicines, which are always cheaper than the innovators' products, help to secure the access to essential medicines. Indeed, WHO has long prompted use of generic drugs of assured quality for this reason.

ii) Quality and Safety

Generic drugs cannot provide expected benefits unless they are of assured quality.

When a generic drug is authorized for marketing, one can assume it is in a good condition for human use, since the health authority should evaluate both innovator and generic drug with the same principles, namely safety, quality and efficacy. Having said that, the safety and efficacy information of innovators' drugs generated by the originators are often being referred in corresponding generic applications to the health authorities. What complicates the case is generic substitution. A generic drug must be therapeutic equivalent to the innovator's drug in order for generic substitution. Otherwise a patient switching from an innovator's drug to a generic drug may experience unexpected therapeutic effect. That could adversely affect the patient's disease control and be fatal in an extreme case. In practice, evidence of bioequivalence (Table 1) is generally the most appropriate proof to substantiate therapeutic equivalence between medicinal products which are pharmaceutical equivalent (Table 1) or alternatives, provided that the excipients they contain are generally

Table 1. Important definitions

Bioavailability (BA)	The rate and extent to which the active substance or therapeutic moiety is absorbed from a pharmaceutical form and becomes available at the site of action. It is usually represented by the Area Under the Curve (AUC) and maximum plasma concentration (C_{max}) shown in a Plasma Concentration Vs Time curve after a single dose of an interested product.
Bioequivalence (BE)	The absence of a significant difference in the rate & extent to which the active ingredient in pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.
Bioequivalence study	Comparing the bioavailability of two or more dosage forms of the same drug.
Essential medicines*	Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility.
Pharmaceutical equivalent**	Medicinal products are pharmaceutical equivalents if they contain the same amount if the same active substance (drug) in the same dosage form, and meet the same or comparable standards (strength, quality, purity). Pharmaceutical equivalence does not necessarily imply bioequivalence. E.g. Marevan® and Coumadin® are pharmaceutical equivalents of warfarin.
Therapeutic equivalent**	A medicinal product is therapeutically equivalent with another product if it contains the same active substance or therapeutic moiety with another previously established product and, clinically shows the same efficacy and safety as that product whose efficacy and safety has been established.

** WHO definition*
*** European Agency for the Evaluation of Medicinal Products (EMEA) definitions*

recognized as safe and carry the same labeling for use.

The issues of generic substitution may not exist or be significant for patients who have never been put on the established innovator drugs. However it is important for patients switching from innovator's drugs to generic drugs. To ensure generic substitution is safe, in other words, to allow generics to maximize their value, health authorities usually require the generic manufacturers to prove the generic drugs, in application, are bioequivalent to their corresponding innovators' drugs. Health authorities of developed countries tend to provide recommendations on the interchangeability of individual generic drugs with corresponding branded drugs for healthcare providers to follow, for example, USA, Australia and Canada.

However, there are still concerns if bioequivalence really can be interpreted as therapeutic equivalence:

- Inadequate number of patients entered into the bioequivalence study
- Only healthy subjects are involved in the studies in existing international guidelines
- Drugs with non-linear PK, e.g. phenytoin (a 5 % difference in plasma concentration may lead to intolerance)
- If either the brand or generic equivalent changes substantially after regulatory approval, the assurance of interchangeability become doubtful
- A generic drug may contain different excipients from the innovator's product. A change in excipients may produce allergens.

III) Patent

The process of pharmaceutical research and development (R&D) is very long, risky, complex and costly. On average, this process takes between 10-15 years and the estimated average cost of developing a new medicine exceeds US$ 800 million [3]. In the course of the R&D process, more than 8,000 compounds are tested on average, of which only one is developed into a potent and safe drug [3]. Undoubtedly, R&D is also a knowledge-based activity. To encourage pharmaceutical R&D, i.e. meeting treatment gaps, a patent system for drugs is thus in place.

Under the Trade Related Aspects of the Intellectual property Rights Agreement (TRIPS) of World Trade Organisation (WTO), WTO Member States need to grant patent protection to innovations including pharmaceutical R&D for a minimum of 20 years. The duration of a patent protection starts when the application is filed. Non-WTO countries may or may not have patent systems in place.

Box 1. Global regulatory approach in determining Bioequivalence@

1. A Bioequivalence testing is done *in vivo*:
   A single oral dose of innovator's (ref) & generic drug (test) are given to healthy human volunteers.
   Drug with low degree variability in Pharmacokinetics (PK), about 12-16 study subjects are required.
   Drug with high degree variability in PK, about 24-36 study subjects are required.
2. Blood samples checked at regular intervals.
3. Calculate the mean ratios of the C_{max} & AUC of the test & ref products.
4. If the 90% Confidence Interval (CI) of mean ratios falls within 0.8-1.25, they are bioequivalent. If the AUC of the ref product is 1, the mean AUC of the test product would be need within 0.9 - 1.10 to be BE. Otherwise the CI would be likely to extend beyond the permitted limits (i.e., 0.8-1.25).
   In reality, products that are deemed to be BE produce mean C_{max} & AUC values that are within about 10% of one another.

@ This analytical approached are adopted by US FDA (http://www.fda.gov/cder), European Agency for the Evaluation of Medicinal Products (http://www.eudra.or/en_home.htm), Australian TGA (http://www.health.gov.au/tga) and Association of Southern-East Asian Nations (ASEAN).

Production or sale of generic drugs during the patent protection period is illegal. Linking patent to pharmaceutical registration is a practice in developed countries such as US and Canada. Recently, this practice has been implemented in China and it will be soon in Singapore. Although the exact procedures used in different countries are not the same, they basically lead to generic drugs not being able to obtain marketing authorization during the patent protection period of corresponding innovators' drugs. The existence of a patent system and the corresponding enforcement are incentives to the innovators to continue investment in R&D. If a patent system does not exist, there will simply be no new drugs developed. Once a patent expires, there should be no limitation for generic drugs to emerge from the market.

Patents are maintained in an impartial way to benefit both the innovators the public. This is not an easy job. Tensions between multinational R&D pharmaceutical companies and healthcare providers, governments and generic manufacturers always exist. There have been global disputes on the length of patent protection, abuse of patent rights, infringement of patent, etc.

One example is a recent scientific study which indicates the WHO's list of essential drugs are rarely under patent in low- and middle-income developing countries. That study was conducted by Dr Amir Attaran regarding the actual level of patenting of essential medicines in 65 countries in Asia, Africa and Latin America, covering a population of over 4 billion people [4]. According to the study, the overall patent incidence for essential drugs in the selected sample of countries including is only 1.4% [4]. Dr Attaran indicated poverty, rather than patents, was the major determinant of access to medicines for people in these developing countries. This view is different from what the WHO has claimed. This issue remains controversial. Dr Attaran's study is the first in a kind of scientific analysis of patenting of essential medicines in developing countries.

III LOCAL ENVIRONMENT

HK is located at the Southern-East part of China. It was an English colony and returned back to China in 1997. Before the handover, HK was already an established city.

i) Health status

Hong Kong has favorable health indices when compared to many developed countries. The infant mortality rate has been declining over the past two decades and reached as low as 2.3 per thousand live births in 2003 and a maternal mortality ratio of 4.2 per hundred thousand live births in 2003 [5]. In 2003, the male and female life expectancies are 78.6 years and 84.3 years respectively, projecting to reach 82 for men and 88 for women in 2031 [5].

ii) Financial status

According to HK Government published data in May 2004, the Gross Domestic Product (GDP) of HK grew at an average annual rate of 3.3% in real terms during the past 10 years and the per capita GDP reached US$23,300 (HK$ 181,500) in 2003. HK's per capita GDP was amongst the highest in Asia. HK was the world's 11th largest trading entity in 2002, although it ranked only 95th (as in mid-2002) in terms of population. HK is also one of the leading financial centres in the world. It ranked 7th largest in terms of foreign exchange transaction in mid-2001, 8th largest in terms of stock market capitalization as at end of February 2004 and 12th largest in terms of external banking transactions as at end-September 2003.

Hong Kong has huge fiscal and foreign exchange reserves, and virtually no public debt.

Nevertheless, HK has suffered from the global economic downturn and local recession in recent years (although the recession starts to turnover in view of the latest economic figures released in September 2004). The unemployment rate was as high as 8.7% during May-July 2003 [5]. The fiscal account has been in red in several consecutive years. HK is

struggling in an economic restructuring or it will be hard for HK to have any further economic growth. HK can no longer rely on the traditional industries, such as service-based economy and entreport to China. The government is proactively exploring areas for development, e.g. knowledge-based economy, a capital of traditional Chinese medicine and tourism.

iii) Healthcare system in Hong Kong

The public sector is dominant in the HK healthcare system. Among these medical services, most of them are managed by the Hospital Authority (HA) which is heavily subsidized by the government. The medical services provided by HA to the public are very cheap (can even be considered as "no" costs to consumers) but with high quality.

Same as many developed area in the world, the public sector is predicted to be unsustainable. The Health Care Reform Consultation Document (or called as Harvard Report) published in December 2000, conducted by a team of experts from the Harvard University of US, indicated HK's healthcare system would soon be unsustainable [6]. Healthcare financing is urgently needed to lessen the government burden, revamp the fee structure of public healthcare sector and allocate the resources better to those who need most ultimately.

iv) Registration of generic drugs

In HK, the registration requirements of innovators drugs and generic drugs are the same, except there is no need to submit clinical documentation for generic drugs. Unlike other developed areas, the Department of Health of Hong Kong (DH) does not request nor evaluate bioequivalence data of generic products in the regulatory review processes at all. DH has no guidance for the healthcare providers in generic substitution. In another words, there is no reassurance on the bioequivalent properties of generic products registered and marketed in HK.

Intellectual property is not sufficiently respected throughout HK. It is the same for pharmaceutical products. There is no patent linkage between the registrations of generics and the patent rights of the innovators' drugs. It is not difficult to discover generic versions of innovators' products which are protected by patents registered with DH and marketed in HK. In fact, the DH refuses to introduce linkage between drug registration and patent, but relies only the applicants of generic drugs to check and obey the patent laws. The existence of infringing products in the market is a reflection of failure of this self-control system.

Matthew Laight of Bird & Bird said, "*In other countries, there is an attempt to balance the interests of originators and generics. But in Hong Kong, there is no reconciliation of the conflicts....The government is granting marketing approval where a patent exists, which in effect is helping generics to infringe.*" [7].

v) Drug utilization practice in HK and expenditure on drugs

Hong Kong has an advanced pharmaceutical market. The healthcare providers welcome latest medications for diseases while the public is very receptive to these products. The per capita expenditure in HK is among the highest in Asia. It was at around US$ 124 in 2003 (approximately 0.5% of GDP) and is set to reach US$ 134 by 2007 [8]. The majority of expenditure is spent on the innovators drugs. Generic drug market penetration is relatively low, at around 10% only [8].

Although DH does not review bioequivalence data in the registration of generics, the fact is the government subsidized body, HA, demands bioequivalence data to decide bulk purchase of generics. HA, accounts for around 70% of all expenditure on pharmaceutical products in HK. HA, through the Government Logistic Department (GLD), initiates government tenders for certain commonly used hospital pharmaceuticals. In the tender invitations, GLD states clearly the generic manufacturers (or their representatives) is required to submit bioequivalence data of concerned generic drugs for evaluation.

Use of a generic drug, which infringes a patent right, could lead to a civil proceeding under existing HK laws. Indeed, the Hong Kong Medical Association (HKMA) advises members to request the suppliers of drugs to ensure that products supplied by them do not infringe the patent laws of HK. HKMA further requests generic drug manufacturers in HK have undertaken to print on their invoices the following statement "THE ABOVE PRODUCTS DO NOT INFRINGE THE PATENT LAWS OF HONG KONG." [9]. By doing so, doctors can hopefully avoid seeking indemnity against claims arising out of the use of offending generic products.

vi) Political and economic concerns

Despite HK being a signatory to all major intellectual property agreements, the level of patent protection of drugs in HK is incredibly low. The lack of enforcement has been an area of concern to the multinational research-based drug industry. Most of the research-based drug companies originated from US, Europe and Japan. Not surprisingly, the lack of enforcement of patent legislation in HK has drawn the attention of European and US governments. The 2003 National Trade Estimate Report, released on 1-Apr-2003 by the office of the US Trade Representative (USTR), highlights positive developments in HK, but does reiterate US concerns in the areas of intellectual property rights projection and the approval process for pharmaceuticals [10]. The report observes any relaxation in HK's intellectual property right enforcement efforts could have negative repercussions for bilateral relations.

The Hong Kong Association of the Pharmaceutical Industry (HKAPI) and the American Chamber of Commerce in HK has issued a position paper to the HK government and it states, "*Hong Kong's continued failure to safeguard pharmaceutical patent rights will discourage investment by international firms and will hamper local innovation. This obviously runs counter to Hong Kong government's stated desire to make Hong Kong the capital of traditional Chinese medicine.*". The member companies of HKAPI have increasingly invested in R&D in HK in recent years. The investment in clinical trials in HK contributed by drug industry is about HK$ 80 million every year [11]. In May 2004, the HKAPI, backed up by the US Consulate in HK and European governments, met with several HK government departments including the Commerce Department to lobby for an enforcement of patent legislation. The negotiation is expected to continue unless HK government makes a move or the industry take a step back to re-allocate resource and investment within Asia.

Following China's entry into WTO, the China State Food and Drug Administration (SFDA) in 2002 introduced provisions in the Drug Registration Regulation to deal with patent linkage. The rules require a company apply to register a drug for clinical studies, production or import to file a letter of guarantee stating that the drug does not infringe a patent [7]. Although such a system is still being criticized by the Western countries, it is regarded as a positive step toward patent protection. HK, being an established region of China, is so much behind the Mainland. The baseline is that HK's competitiveness will drop if HK does not make sufficient improvement in this aspect.

IV DISCUSSION

The value of generic drugs cannot be denied. Being offered at much lower prices than the innovators' drugs, they have a significant role in improving the access to medicine especially for those

in the least developed, and low- to middle-income countries. Although HK is a relatively wealth city, the existence of generic drugs is important. While the demand for medicines is expected to increase because of aging, the facts such fiscal deficit, unsustainable public healthcare system, slowly recovering local economy, increasing amount of citizens falling in the low income category mean the society needs cheaper and safe drugs with good quality. It is thus a public interest to have up-to-standard generic drugs available in Hong Kong.

A registration of a generic drug in HK does not necessarily imply generic substitution is suitable. The interpretation for physicians seems to be "*The generics are safe for new cases (patients), but not necessary in generic substitution*". We trust the local government does not really mean to disseminate such message out to the healthcare providers. However the existing system cannot secure the suitability of generic substitution -- the most important aspect of usage of generic in HK, is a fact and pending for improvement. Otherwise generic drugs lose their major function in HK. The DH should as soon as possible include bioequivalence data in the regulatory review of generics seeking registrations and provide guidance for healthcare providers in generic substitution. It would be more efficient and feasible for DH to centrally evaluate bioequivalence and make recommendations in generic substitution.

With very good health status, the need for cheaper medicines should not be an excuse for violation of laws in HK. Generic drugs, which infringe the patents of corresponding innovators' drugs, should not be used. One may argue it is the public interest to use cheaper generic drugs and the WHO encourage use of generics as well. This is not entirely correct for HK and it is a misuse of WHO position. Under no situation should violation of laws be encouraged. Use of generic use is subjected to conditions - the patent protections of corresponding innovators' drugs have finished. WHO always respects the intellectual property rights and TRIPS which has a wavier system. A country, having no or limited access to the "essential medicines", is allowed to manufacture or import generics for citizens under the compulsory licenses of TRIPS. HK announced it would only use this wavier for emergencies or extremely urgent situations and 23 developed countries with WTO announced voluntarily that they would not use this wavier system to import infringing generics [12].

Moreover, being an international city, HK should respect intellectual property right so as to secure position internationally and be attractive to foreign investment. Under the globalization and rapid development of surrounding cities, HK's competitive advantages have dropped undoubtedly and can no longer reply on the traditional industries. The city has been struggling to find a way to survive and grow. Two of the government proposals for future HK are developments of knowledge-based economy and capital of Chinese medicines. With the existing level of enforcement of patent legislation, HK's ability to attract foreign investment and expertise is doubtful. As already indicated by the research-based pharmaceutical industry, investment at least in the area of clinical trials, will probably lose if the government shows no improvement in the enforcement. At the same time, ones need to be aware both Singapore and Taiwan governments have announced they are developing and positioning themselves as the centers of excellence in clinical research in the Asia-Pacific region.

The government has claimed the innovators can initiate litigations if they found infringement of patents. Since there are extremely limited concerned litigations on-going in HK, it implies infringement of patents is not severe in HK and introduction of patent linkage is not necessary. Such a claim is incorrect. It is hard to believe the government does not realize the sale of an innovator's drug in a small area like HK is very little compared to the global sale. Initiating an expensive litigation for the sale of the drug in HK is usually not justified. Using this kind of approach to manage complaints from the pharmaceutical innovators is rather unwise and shortsighted. More importantly litigations should not be encouraged. Litigations actually cost a lot to the taxpayers. Moreover they could be misused by the innovators to temporize generic competitors and eventually affect the public interest. HK needs to establish a linkage between drug registrations and patent, in which the patent system has low chance for the innovators to abuse. Simultaneously enforcement of patent protection must be done in order to maintain HK's competitiveness and support further grow.

In short, the generic drugs having assured quality & efficacy, and not infringing patent rights should be used in order to lessen the healthcare cost, especially in the public sector. However the existing local environment does not encourage a rational use of generics. Requiring the healthcare providers to assess generic substitution without official guidance is unacceptable nowadays. Expecting the profit-driven generic companies to behave themselves in a jurisdiction without enforcement of patent laws and with low respect of intellectual property is somewhat unrealistic. The outcome is also highly questionable. The government can help to encourage proper use of generic drugs by introducing a requirement of evaluation of bioequivalence data in the registration of generic drugs and issuing guidance in generic substitution for individual generic products, at least for new generic products; implementing patent linking with registration of pharmaceuticals; and enforcing patent legislation. Before these improvements are made, there is no an easy answer for the topical question. Individual healthcare providers are unfortunately forced to do evaluation for individual generic drug and make their own judgments.

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Helen Wong is currently the section editor in Society Activities of HKPJ. She is now working in the field of Clinical Research in a multinational company.

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Overview of R&D / Clinical Trials in China and its Future Impact in Hong Kong

Chiu, Terry

I INTRODUCTION

Recent years, many multinational drug manufacturers have started to perform their product researches and clinical trials in China. Astra Zeneca, Eli Lilly, Novartis, Pfizer, Roche have set up either clinical trial centers or R&D facilities in the mainland. It can be implied that there must be attractive points for them to do so. However, we can also see that these actions are not without risks. Nevertheless, owing to CEPA, procedures are now being developed for mutual recognition of clinical trial data for traditional Chinese medicine between HK and China. Such a policy is expected to be extended to western drugs. Existing hurdles to China market may be overcome and Hong Kong may be able to take advantage of it.

II ATTRACTIVE ENVIRONMENL - LARGE POTENTIAL MARKET

One of the attractive points of performing clinical trials in China is the large treatment-naive patient pool [1]. In the western countries, patients are often treated with a combination of compounds. Suitable patients could not be easily recruited due to the potential drug-drug interactions between concurrent administered drugs and compounds to be investigated. In contrast, western medicines have relatively few been accessed in Chinese patients. Hence, there are a large number of suitable subjects in China [1].

On the other hand, it is generally misconceived that clinical trials performed in Asian countries are inferior to those of their western counterparts. However, this is not the truth. Many large multinational R&D based drug manufacturers concede that investigators in Asia are of high standard. General enthusiasm among investigators in Asia, particularly with China, scores particularly well. They are generally regarded as "well educated, motivated, talented, hard-working". Language problems with using English are not prominent. Trials in several areas are even performing better than those conducted in Europe and US [2].

Cost is always an important factor during drug development. It is estimated that a clinical trial can consume up to 1 billion US dollars in western countries. If clinical trials are performed in China, this cost can still be cut down by one-third despite the fact that additional indirect expenses like translation and training might be required.[1]

The most attractive point for drug manufacturers to perform their researches and clinical trials in China is the large potential market. Although the Chinese are just spending US$6 on prescription drugs a year at this moment as compared to the westerners who are spending about US$500. China is now within the top 10 markets in the world [1]. Growing economy, increasing awareness and better knowledge towards western medicine give the country plenty of room for growth in market size. It is generally foreseen that the market in China will be bright in the future. Research and development is thus seen to be favorable in China.

III REGULATORY HURDLES

However, although improving in progress, various regulatory hurdles are found in the process of research and development. Various drug manufacturers are always criticizing the slow process of approval of clinical trials. While it requires only three months for Singapore authorities to review an application, China SFDA requires almost a year for evaluation. Limited staff resources with heavier and increasing workload are the major reasons why applications in China proceed slowly [1].

Besides, it also lacks international trial sites. Compared with the fact that there are over 30 sites with international standards in Japan, the current 40 sites for the whole Mainland China may seem a bit too few for a country of its size [2].

Although it is predicted that China will grow into the third largest market within this decade, following the US and Japan, few Chinese patients have had the money to pay for branded western drugs [2]. Although there is a huge population in China, the average income is not high. Average annual income of a typical Chinese worker in the cities is around US $1000, which is one-tenth of that of a western worker. The affordability of Chinese in the new branded western drugs is hence questionable.

Also, intellectual property protection is still an issue. Branded western drugs are not guaranteed patent protection in the Mainland China. Generics for Viagra (Pfizer) and Avandia (GSK) have both been legally sold in the mainland. Intellectual property protection is vital to the business of R&D industries like pharmaceutical industry. Thus, disrespect to western intellectual rights is thus a critical concern [1].

In addition to risks from generics, severe counterfeit problems are a serious concern for those research based companies [1]. The enforcement of patent protection by the Chinese authority is not yet uniform, and has long been criticized by multinational companies.

IV IMPACT IN HONG KONG

Panel 1. Advantages and hurdles of conducting clinical trialss

THE ADVANTAGES	THE RISK / HURDLES
• Large treatment-naive patient pool • Large potential market • Low investment cost • Well educated scientific workforce • Comparable (or even better) standard of investigation	• Protectionism • Regulatory hurdles - slow process of permission • Counterfeit drug • Strict trial requirement • Low ability to afford high-price new western drug • Extra provision of specialist trial equipment, training and translation

It is generally accepted that China is too large a market to be ignored in the future. However, some companies may regard that the environment is still not mature enough to place heavy investment aggressively due to various reasons listed above. As stated in the Annex 6 of CEPA, mutual recognition procedures for clinical trial data of traditional Chinese medicine and medicinal products between Hong Kong and China are now being developed. This policy is expected to be extended to western medicine in the future. In this case, Hong Kong may have an important role in overcoming some of the hurdles existing in China, if policy of mutual recognition of clinical trial data is extended to western medicine in the coming future.

One of the fatal points in the clinical trial process in the mainland is the slow approval time, as mentioned above. It can take as long as 12 months for approval [1]. Hong Kong, on the other hand, has a higher efficiency in dealing with this process. Normally it takes only about three to six months for the review. Since patent protection period is limited to 20 years in China [3], time for regulatory approval should be as short as possible. Also, as compared to the Mainland, Hong Kong has more investigators who are experienced in large international trials. This advantage would probably also result in a faster process.

However, there is also trade off for choosing Hong Kong as the stepping stone to the Mainland market. Being a city with living standards comparable to western countries, it will also be costly for conducting clinical trials. Companies would thus be unable to take advantage of the low investment costs in the Mainland China.

Moreover, western medicine is widely practiced in Hong Kong. Therefore, suitable subjects without potential for drug-drug interactions for trials may be more difficult to find. These factors hinder the role of Hong Kong as the clinical trial stepping-stone to the China market.

Terry Chiu is a CUHK Pharmacy student who has been given opportunities to work in the pharmaceutical industry.

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The Growing Importance of Cost Effectiveness

Choi, Kwok-Ho

I INTRODUCTION

The concept of pharmacoeconomics, or cost-effectiveness of pharmaceutical products, is gaining rising concern around the world and is becoming the fourth hurdle to market entry. This would greatly lengthen the time taken for new drugs to complete pre-marketing clinical trials. This would also increase the costs to provide relevant analysis and information. Balancing such huge cost with sales would become a great problem to pharmaceutical companies. It is therefore important for regulatory staff to keep themselves update in pharmacoeconomics, its trends of development and effect in the future.[1]

II COST EFFECTIVENESS IN PRACTICE

The history and development of pharmacoeconomics concept are summarized in Table 1.

i) The United Kingdom (UK)[2]

UK is one of the leading countries in the world to develop mechanisms for a highly consultative and sophisticated appraisal of the cost-effectiveness of medicine. The National Institute for Clinical Excellence (NICE), established in February 1999, was the vehicle to provide determinations to the cost-effectiveness of new technologies. NICE appraises the clinical benefits and the costs of those interventions notified by the Secretary of State and makes recommendations regarding the cost-effectiveness to the National Health Services (NHS). Either positive or negative appraisals would be given to a particular pharmaceutical product. Negative appraisals mean that a medicine will not be stocked in the hospital pharmacy. Therefore, NICE takes an important role for the market entry of the pharmaceutical products in UK.

NICE is required to take into account certain factors including "the degree of clinical need" of patients to whom the intervention is directed, the broad balance of benefits and costs, the effective use of available resources, any guidance of the Secretary of State on the resources likely to be available and the government's healthcare priorities. Data for analysis are submitted by the pharmaceutical company and other "stakeholders" such as patient groups and professional bodies, which would be the subject of evaluation by NICE's Appraisal Committee.

ii) The United States (USA)[2,3]

The US does not have a national health care system like that of National Health Services (NHS) in UK. Instead, the US health care system is a patchwork of public and private organization, funded by hundreds of public and private third-party payers.

Table 1. Milestones for the establishment of cost-effectiveness to market entry [2]

Year	Event
UK	
1985	Establishment for the creation and revision of "Blacklist"
Early 1999	Additional terms of reference for reimbursement decision
Feb 1999	Establishment of National Institute for Clinical Excellence (NICE)
USA	
2000	Establishment of Academy of Managed Care Pharmacy (AMCP) formulary guidelines
2003	Medicare Prescription Drug, Improvement and Modernization Act of 2003

Each payer can manage their own formularies with different drug coverage. Under the recently passed Medicare Prescription Drug, Improvement and Modernization Act of 2003, the Medicare outpatient drug benefit (Part D of the Medicare program) will offer coverage for up to 41 million elderly over 65, end stage renal disease patients and disabled beneficiaries and it is estimated to contribute to one-third of the total US prescription drug spent by 2008. Centre for Medicare & Medicaid Services (CMS) is responsible for the reimbursement to various private health plans to deliver drug benefits to the beneficiaries. Therefore, CMS can exert controls to private health plans by controlling the criteria required for reimbursement.

CMS has clearly articulated that it may deny payment or reimbursement for FDA approved drugs for a number of reasons, including "costly to the Medicare program". Besides, CMS has drafted a set of proposed rules explicitly authorizing participating plans to consider cost in making formulary decision in addition to clinical evidence, showing that pharmacoeconomics is an important concern during reimbursement. The ability to design cost-effectiveness formularies will be one of the most critical factors determining whether plans will participate in the Medicare drug benefit. Whether the drug is cost-effective or not would decide whether that drug would appear in plans that will participate in the Medicare drug benefit, and hence, the usage of the drugs. Therefore, safety, efficacy and quality decide whether the drug can get approval from FDA and cost-effectiveness decides whether the drug will be used.

Panel 1. Parameters for the analysis of cost-effectiveness by NICE

Direct Cost
Indirect Cost
Cost per Quality Adjusted Life Year (QALY)

iii) Hong Kong [5]

In January 2005, the draft proposal of Hospital Authority Standard Drug Formulary was published for public consultation, which can be thought of as a milestone for the establishment of the concept of cost-effectiveness in Hong Kong.

The Draft proposal of Hospital Authority Standard Drug Formulary contains two categories of drugs, namely General Drugs and Special Drugs. General Drugs refer to drugs with well-established indications and effectiveness which are available for general use as indicated by the patients' clinical conditions and comprises around 85% of the drugs within the Formulary. Special Drugs refer to drugs which are to be used under specified clinical conditions with specific specialist authorization and comprises less than 15% of the drugs within the Formulary.

Three criteria taken into account for the inclusion of drugs into the Standard Drug Formulary include the disease prevalence, available evidence on efficacy and safety, and the comparative cost effectiveness. Those failed in suiting those criteria include drugs proven to be of significant benefits but extremely expensive, those having preliminary medical evidence, those with marginal benefits over available alternatives but at significantly higher costs and life-style drugs.

It is obvious that cost-effectiveness is an important consideration for the inclusion of drugs in the Standard Drug Formulary. Being the largest customer of pharmaceutical products in Hong Kong, the concern of Hospital Authority on cost-effectiveness of drugs will greatly influence the marketing strategies as well as that of drug development for the pharmaceutical industry.

III VARIOUS METHODS OF ECONOMIC EVALUATION [4]

There are various methods of economic evaluation for the pharmaceutical products. The characteristics of individual parameters are discussed in table 2.

IV THE NEW CHALLENGE

The concept of cost-effectiveness emerged in the United States since the Medicare Prescription Drug, Improvement and Modernization Act of 2003. It is expected that more guidelines and recommended methods of economic evaluation will be published. Regulatory staff should keep themselves updated with these new publications, especially those related to Part D of the Medicare program as well as USP draft model.

Cost-effectiveness will become an indispensable component of the medical system in the future. It will be a great challenge for the pharmaceutical industry, no matter what the pre-marketing clinical trials or the marketing strategies of their new products are like.

Table 2. Various methods of economic evaluation

Paramete	*Characteristics*
Cost analysis	• Identify all the direct and indirect costs of a particular disease, including medical cost and production loss. • Generate a total cost of a particular disease to measure for the value of prevention and treatment strategies.
Cost-effectiveness analysis	• Compare treatment alternatives where the output or consequence is assessed in natural units or health effects. e.g. cases successfully treated, years of life gained. • Can be used to compare treatment alternatives with different therapeutic outcomes.
Cost-minimization analysise	• Compare the costs of treatment alternatives that are therapeutically equivalents • Consider treatment alternatives with the lowest cost e.g. brand products vs generic products
Cost-utility analysis	• Compare treatment alternatives where outcome is expressed in terms of quality of life e.g. Quality-adjusted life-year (QALY) = total life-years gained from treatment x utility value • Utility value reflects the relative values individuals place on different states of health.
Cost-benefit analysis	• Compare the costs and benefits of treatment alternatives in monetary terms. • Fail to consider other intangible benefits, such as feeling better and healthier.

Choi Kwok Ho is a CUHK Pharmacy student who has been given opportunities to work in the pharmaceutical industry.

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β-thalassaemia Major and Iron Overload

Wong, Ivy

2 CE Units

I THE THALASSAEMIAS

i) Introduction

The thalassaemias are a heterogeneous group of genetic disorders. Defective synthesis of one or more globin chains brings about partially or completely suppressed production of normal adult haemoglobin (HbA, $\alpha_2\beta_2$). Hence, anaemia results. Several types of thalassaemias have been described in relation to the defective chain. The more common, severe and clinically important types are the α- and β-thalassaemias. We shall only discuss the β-thalassaemias here in this article.

Firstly discovered in Mediterranean countries and commonly found in Middle East and South East Asia, β-thalassaemias are now known to affect people throughout the world, owing to the continual migration of populations. It has been estimated that over 100 million people in the world are heterozygous β-thalassaemia carriers and probably over 100,000 newborns are homozygous β-thalassaemia carriers every year[1]. In Hong Kong, it is estimated that 8.5% of the population (about 550,000 individuals) are heterozygous β-thalassaemia carriers and there are about 400 β-thalassaemia major sufferers[2]. If not diagnosed and adequately treated, most patients with β-thalassaemia major die before the age of five years due to insufficient erythropoiesis. However, the complications in consequence of severe anaemia are preventable or treatable with recommended treatments, which will be discussed later in detail. Therefore, the overall prognosis of the disease is progressively improved.

ii) Pathophysiology and Genetic Basis of β-thalassaemias

Haemoglobin transports oxygen from the lungs to tissues. This specialised molecule is made by four globin chains arranged in matching pairs.

Several types of haemoglobins exist, but only HbA ($\alpha_2\beta_2$) is dominant in normal adults with another minor component named HbA_2 ($\alpha_2\beta_2$)[3].

Two genes, one from each parent, code for the β-globin chain. In the case of heterozygous β-thalassaemia (β-thalassaemia minor), only one allele is affected. The normal β gene still contributes to sufficient stable β-globin production and hence carriers are generally asymptomatic with only mild hypochromic and microcytic anaemia, which normally has no clinical importance[3].

On the other hand, patients with β-thalassaemia major inherit two defective β-globin genes from their parents. This leads to β-chains deficiency and the excess β-chains precipitate in the red cell precursors. Red cell maturation is disturbed and ineffective erythropoiesis occurs. Precipitation of excess α-chains occurs in mature red blood cells as well, resulting in haemolysis. The kidneys, being stimulated by the anaemic state, manufacture more erythropoetin. This causes bone marrow expansion and in turn leads to significant deformities of the skull and long bones. Due to the entrapment of the abnormal red blood cells, splenomegaly may occur. Blood shunting through the enlarged spleen increases plasma volume and aggravates the anaemia.[4] The consequences are that β-thalassaemia major sufferers undergo severe anaemia and symptoms arise early at the age of 3-6 months[3], which include lethargy, lost of appetite, and paleness. If appropriate diagnosis and treatments are not initiated, these patients generally cannot survive to the age of ten.

II THERAPIES IN β-THALASSAEMIA MAJOR

i) Blood Transfusion Therapy

To correct the severe anaemia in β-thalassaemia major, so as to overcome ineffective erythropoiesis, avoid bone deformities and allow normal growth, regular blood transfusion is the mainstay of treatment.

Once the diagnosis of β-thalassaemia major is established, blood transfusion should be initiated and repeated once every 4-6 weeks. The haemoglobin levels for pre- and post-transfusion are targeted at above 9-10.5g/dL and not more than 15g/dL respectively[3].

Blood products for transfusion to thalassaemia individuals are carefully selected from healthy donors. Screenings are to be done to exclude transmissible diseases such as hepatitis B and C, AIDS and syphilis. Only leucoreduced packed red cells should be used to avoid adverse reactions caused by contaminating white cells and to prevent platelet alloimmunisation. Washed red cells, free from plasma protein, may be favourable for patients allergic to transfused blood.[3]

ii) Splenectomy[3]

Hypersplenism is a condition in that the spleen becomes overactive to break down normal red blood cells

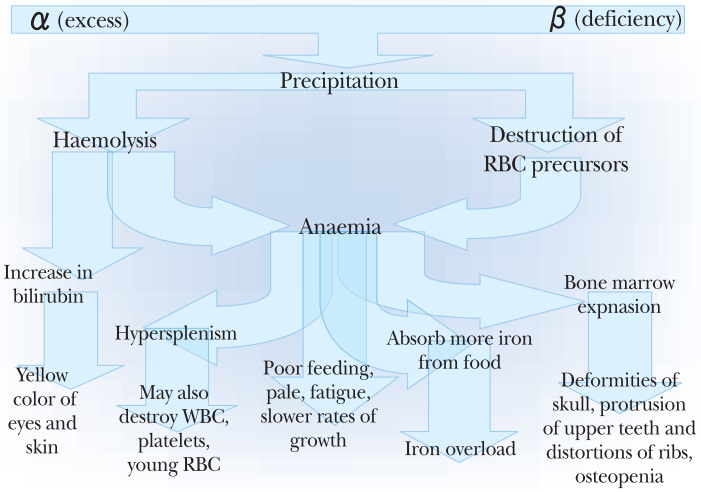

Figure 1. Consequences of excess free α-chains production

Watsons Your Personal Store is the largest health and beauty retail chain in Asia operating over 900 stores and 680 pharmacies in 9 markets - Hong Kong, Taiwan, Mainland China, Macau, Singapore, Thailand, Malaysia, the Philippines and Korea.

In Hong Kong, Watsons has won a number of customer service awards and operates over 160 stores with 2,000 employees. Watsons is Hong Kong's largest pharmacy chain with 50 licensed pharmaceutical counters, served by 100 pharmacists, while other stores station a total of over 125 professionally trained health and fitness advisors.

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received from transfusion. As a consequence, the patients require more blood to be transfused every time. In order to reduce blood requirement and transfusional iron overload, spleen removal may be considered, especially in those with sub-optimal chelation therapy. In addition, patients with splenomegaly causing possible splenic rupture or left upper quadrant pain may also consider splenectomy. Since a hyperactive spleen destroys white blood cells and platelets as well, leucopenia and thrombocytopenia are probable outcomes. Patients experiencing recurrent infections or bleeding are possible candidates of the surgery.

In practice, only patients over five years of age are advised of splenectomy on account of the increased risk of infections afterwards.

The major concern following splenectomy is overwhelming sepsis which is the greatest threat to face within 1-4 years after surgery.

Vaccination is important in prophylaxis of infections after splenectomy. Vaccines that should be given before the surgery include *Haemophilus influenzae* vaccine and meningococcal polysaccharide vaccine. Streptococcus pneumoniae infection is one of the most prevailing in asplenic patients. Therefore pneumococcal vaccine should be given at least 2 weeks before splenectomy and then again in 3-5 years. Influenza virus vaccine administered yearly is also beneficial.

Chemoprophylaxis with oral penicillin 250mg twice daily (125mg twice daily for children under two years) is recommended in all children under five years to reduce the risk of postsplenectomy sepsis. Alternatives include amoxicillin, erythromycin and co-trimoxazole. The value of prophylactic antibiotics after five years of age is uncertain. In these patients, some physicians may utilize long-term chemoprophylaxis while others may merely apply the practice for two years after splenectomy. As developments on new vaccines continue and bacterial antibiotic resistance is ever changing, the use of prophylactic antibiotics may need to be regularly re-evaluated.

III IRON OVERLOAD IN β-THALASSAEMIA MAJOR

i) Iron Overload

Iron overload occurs as a result of regular blood transfusion. In poorly transfused patients, increased iron absorption due to erythropoetin activity can cause iron overload too.

In normal individuals iron atoms are bound to plasma proteins like transferrin or ferritin. However, in cases of iron overload, these molecules saturate and the highly reactive free iron are allowed to react and produce free radicals, which pose damages to organelles, DNA as well as lipid membranes.[3]

Many major organs, for instance, the heart, liver and endocrine glands, are damaged by accumulated iron if the excess is not chelated. Significant complications such as cardiac problems, hypoparathyroidism, hypothyroidism, hypogonadism, abnormal growth, diabetes as well as liver disease may emerge as early as before ten years of age.

ii) Iron-chelating Therapy: Desferrioxamine

Of all the iron-chelating agents, desferrioxamine (Desferal® or deferoxamine) is supported by the most abundant clinical data and experience. Desferrioxamine is a siderophore, which is naturally occurring, extracted and purified from the microbe *Streptomyces pilosus*. At physiological pH, one desferrioxamine molecule binds to one iron atom and forms a highly stable iron complex, ferrioxamine. However, in clinical applications, only about 10% of the drug binds to iron before elimination from the body[3]. Iron released after the breakdown of red cells in macrophages is excreted in urine after chelation, whereas iron chelated from the liver (the largest iron store in the body) is excreted in bile[5]. In practice, desferrioxamine is to commence after the first 10-20 transfusions or when the ferritin level rises above 1000 μg/L[5]. The recommended administration approach is by slow subcutaneous infusion of a 10% desferrioxamine solution (prepared by dissolving a 500mg vial of desferrioxamine in at least 5ml of water for injection) over 8-12 hours using an infusion pump for 5-7 days per week, at a daily dose of 20-60mg/kg[5].

The role of vitamin C (ascorbic acid) in β-thalassaemia major drug therapy is to reduce Fe^{3+} to Fe^{2+} ions, which are more mobile in the body and become chelated more easily[3]. In order to increase iron removal, oral vitamin C should be taken 30 minutes to 1 hour after the start of desferrioxamine infusion and skipped on the day without desferrioxamine administration[6]. Treatment should commence within a few weeks after the initiation of desferrioxamine. The recommended dosage is 50mg per day orally for children under ten years of age and 100mg per day for older children. Vitamin C supplementation may not be essential for patients who regularly intake orange or fresh juice[3].

iii) Efficacy of Desferrioxamine

The beneficial effects of desferrioxamine on survival and fatal complications in β-thalassaemia major have been demonstrated in several studies. Both studies from Italy[7] and Hong Kong[8] suggested that early initiation of chelation therapy improved patient survival. One study revealed that adequate amount (in proportional to the transfusional iron load) and early use (low transfusional iron load before initiation of chelation therapy) of desferrioxamine reduced body iron burden, as indicated by decreased hepatic iron store measurement, and also reduced the risks of fatal complications such as cardiac diseases, diabetes as well as early death[9]. Another study showed that desferrioxamine treatment maintaining serum ferritin level below 2500 μg/L was correlated with high cardiac-free survival rates[10].

iv) Alternatives to Subcutaneous Infusion

In serious situations of iron overload in which cardiac complications like cardiac dysrhythmia or failing ventricular function arise, continuous intravenous infusion of desferrioxamine may be more beneficial than periodic infusions because it reduces the exposure to toxic free iron (non-transferrin-bound iron), which returns to pre-treatment levels within minutes of stopping a continuous intravenous infusion[11].

In a recent long-term follow up study, a survival rate of 61% at 13 years was achieved in high-risk patients using continuous intravenous infusion. Markedly reduced iron stores, reversed cardiac dysrhythmias and improved left ventricular ejection fraction were achieved with this iron chelation strategy[12].

One study demonstrated that injecting desferrioxamine subcutaneously twice a day may be as effective as subcutaneous infusions in terms of urinary iron excretion[13]. However, no study provides the data on outcome of survival or complication rate.

v) Monitoring Iron Overload During Desferrioxamine Treatment

To assess the efficacy of iron chelation treatment and to avoid complications of excessive therapy, iron overload should be monitored closely. The initial effectiveness can be indirectly estimated by measuring urinary iron excretion and serum ferritin level. However, inflammation, ascorbate status and hepatitis may cause variations in measurement. The long-term efficacy of desferrioxamine treatment may be more accurately assessed by measuring hepatic iron stores using liver biopsies or SQUID-biosusceptometry. Magnetic

resonance imaging (MRI) is appropriate to evaluate organ iron deposition, especially in the heart.[1] It is suggested that both the risks of deferrioxamine toxicity and the risks of complications from iron overload can be minimized if maintaining the liver iron concentration at 3-7mg iron per gram of liver (dry weight)[6]. If measurement of liver iron concentration is not feasible, serum ferritin level may be used to assess body iron burden. Studies found that maintaining serum ferritin level of below 2500 μg/L was associated with 100% survival rate without cardiac disease in patients after 10 years of chelation therapy, compared to only a 50% survival rate in those with serum ferritin level above 2500 μg/L[10].

vi) Complications of Desferrioxamine Administration[3]

Upon desferrioxamine administration, local skin reactions such as itching, erythema and induration are frequent. Infection with *Yersinia enterocolitica*, which exploits ferrioxamine for growth, is rare but serious. It would be rational to withhold desferrioxamine treatment when an unexplained fever develops until an identifiable cause is detected.

Complications associated with desferrioxamine overdose are minimized by dosage adjustments. Reported consequences of overdose consist of toxic effects on the eyes and ears. Growth retardation and abnormal skeletal growth may occur in young children at higher doses. Renal impairment and interstitial pneumonitis are possible at very high doses.

vii) Iron-chelating Therapy: Deferiprone

Despite desferrioxamine's established efficacy, its expense and the inconvenience of long-term subcutaneous administration have led to the development of oral iron-chelating agents. Deferiprone (Ferriprox®, Kelfer®, L1) is now the only orally active iron-chelator clinically employed. Belonging to a group of bidentate chelators, three molecules of this α-ketohydroxypyridone attach to one iron atom. At usual dosages of 75mg/kg/day in 3-4 divided doses, only around 5% of deferiprone binds to iron before being eliminated. Unlike desferrioxamine, iron is excreted through urine almost exclusively.[3] This oral iron-chelator is now licensed for sale in India and Europe as a second line therapy for individuals contraindicated or intolerant to desferrioxamine[14]. For patients with poor compliance to desferrioxamine, repeated counselling and investigation of alternative drug administration regimes should be attempted to optimise therapy before initiating deferiprone.

viii) Efficacy of Deferiprone

Early studies showed that deferiprone was comparable with desferrioxamine in increasing urinary iron excretion[15], normalizing serum ferritin, and reducing tissue iron, including hepatic iron[16,17]. However, later studies showed a disappointing result. In the long term use of deferiprone, 50% of patients' hepatic iron content cannot be controlled below 15mg iron per gram of liver, a level associated with a higher risk of cardiac disease.[18] For the reduction in serum ferritin, deferiprone (25mg/kg Q8H) was found to have similar efficacy to subcutaneous desferrioxamine (50mg/kg infused over 12 hours per day for 5 days in a week)[19]. Another study comparing these two iron chelators at the same dosages showed similar results but better patient compliance with deferiprone[20]. Concerning deferiprone's cardiac effects, one study found that it was more effective than subcutaneous desferrioxamine in removing myocardial iron, and brought about higher ejection fractions[21]. A recent retrospective study showed that deferiprone had greater cardioprotective effects than subcutaneous desferrioxamine[22]. The reason behind is that deferiprone has a higher cell penetration than desferrioxamine to chelate iron from the heart. Furthermore, deferiprone is capable of indirectly reducing myocardial iron uptake through mobilisation of iron from transferrin[23]. Nevertheless, due to the small sample sizes of the above studies, further clinical trials involving more patients are essential to establish the efficacy of deferiprone.

ix) Safety of Deferiprone

Arthralgias, as reported in many studies, are the most common adverse effects[24,25,26,27]. Patients experiencing the side effect may continue deferiprone with or without analgesics. The most serious adverse effect is agranulocytosis (absolute neutrophil count (ANC) <500/mm^3), which occurred in less than 1% of patients with about 5% of patients undergoing milder forms of neutropenia (ANC 500-1500/mm^3) in some studies[24,27]. Routine ANC monitoring is recommended especially if there are signs of infection. Neutropenia and agranulocytosis are reversible upon discontinuation of deferiprone but the drug should not be reintroduced. In contrast to an older study[28], recent data from a one-year clinical trial demonstrated that deferiprone was not associated with hepatic fibrosis progression[29]. Other common adverse effects reported include nausea and vomiting, zinc deficiency, transient rises in serum ALT levels and immunologic changes[24,27].

x) Iron-chelating Therapy: New Strategy

Combined iron chelation therapy with desferrioxamine and deferiprone may be a new therapeutic strategy. The rationale behind is that deferiprone, which has a lower molecular weight and higher lipophilicity than that of desferrioxamine, enters cells more easily to chelate intracellular iron, which is in turn transferred out to the plasma where desferrioxamine exerts its effect preferentially[30]. Several small studies have shown that combined therapy may be more effective than standard dosages of desferrioxamine or deferiprone alone in reducing serum ferritin level and increasing urinary iron excretion[31,32,33]. Therefore, for patients who cannot comply with desferrioxamine infusions a few days per week, or for those whose target iron store levels cannot be achieved by deferiprone alone, combining deferiprone at its standard dosage with additional doses of desferrioxamine infusion may be feasible. However, large and long-term prospective trials are still awaited to offer more data on the safety and efficacy of this strategy.

IV COMPLICATIONS OF IRON OVERLOAD IN β-THALASSAEMIA MAJOR

As mentioned previously, iron overload due to regular transfusion or increased iron absorption from the gut may generate free radicals and cause damage to major organs including the heart, liver, endocrine glands such as the pancreas, thyroid glands, parathyroid glands as well as pituitary glands. Therefore, complications like cardiac disease, liver failure, diabetes, hypothyroidism, hypoparathyroidism and hypogonadism follow when the chelating therapy is sub-optimal or not well complied. Osteoporosis may occur as well.

These complications can be controlled by an intensified chelation therapy to lessen the body's iron burden, and by the rational utilisation of drugs.

i) Cardiac Complications

Iron overload related complications on the heart are the leading causes of death and one of the major causes of morbidity in β-thalassaemic patients. Left ventricular hypertrophy and conduction disturbances are often found in patients on irregular transfusion schemes, in whom the transfusion was unsuccessful or those who have not received chelation therapy, resulting in congestive heart failure and arrhythmia by the mid-teens[6].

Drug treatments on cardiac complications in these patients are similar to those employed in non-thalassaemic patients. Angiotensin converting enzyme inhibitors and diuretics are used in congestive heart failure while beta-blockers and digoxin may be beneficial in

arrhythmias. Amiodarone should be used with caution for supraventricular and ventricular arrhythmias, as hypothyroidism is a complication in thalassaemic patients per se.[3]

ii) Growth and Delayed Puberty

Endocrine abnormalities are among the most common complications of thalassaemia. It is difficult to determine the prevalence of endocrine complications due to the differences in the age when iron chelation therapy is initiated. Table 1 summarises the incidence rates as found in various studies.

iii) Growth[36]

Regular blood transfusion produces normal pre-pubertal linear growth in thalassaemia patients, but at the same time, repeated use of desferrioxamine may produce a toxic effect on the bones, which is a major cause of growth retardation[37,38,39]. Anaemia, folate deficiency, hypersplenism and iron overload in tissues are well-known reasons of impaired growth in patients receiving irregular transfusion. Growth hormone deficiency, diminished responses to either growth hormone or growth hormone-releasing hormone are also contributing factors. In these cases growth hormone may be prescribed[40]. However, this hormonal treatment should be used cautiously because reduced insulin sensitivity and abnormal glucose tolerance may result.

iv) Delayed Puberty and Hypogonadism[36]

Delayed puberty and hypogonadism are the most common endocrinological findings in iron overload. Excess iron leading to sex organs and pituitary glands damage may cause primary and secondary hypogonadism in some thalassaemia patients. Studies showed that female patients may suffer from primary and secondary amenorrhoea. Other possible causes of hypogonadism include liver disorders, chronic hypoxia, diabetes mellitus, and zinc deficiency.

Hormonal replacement therapies, either intramuscular depot-testosterone esters for males or oral oestrogens for females, may be useful for pubertal disorders in thalassaemia. In cases of no breakthrough bleeding, low dose oestrogen-progesterone treatment is an option for young females[3].

v) Hypothyroidism[3]

Hypothyroidism is a condition infrequent in patients with satisfactory treatment but common in the severe anaemics and/or iron overloaded thalassaemics.

This complication usually arises between the ages of 11-20 and is slightly more frequent in females. Thyroid function monitoring should be done annually, starting at the age of 12 years. T_4 or free T_4, and thyroid-stimulating hormone (TSH) levels are the main investigations, together with the thyrotrophin-releasing hormone (TRH) test and TSH response test. Treatment involves thyroxine supplementation.

vi) Impaired Carbohydrate Metabolism

Iron deposition within the liver increases insulin resistance and results in impaired glucose tolerance and diabetes mellitus. Reduced insulin secretion due to either exhaustion of beta-cell or/and iron deposition in islet cells also contribute to the complications. The pathogenesis resembles that of type 2 diabetes in that, reduced insulin sensitivity triggers compensatory increases in insulin secretion before the beta-cells exhaust.[41] However, the age of onset in thalassaemia patients is usually after the age of ten with the highest prevalence between age of 16-20[34]. Therefore, annual oral glucose tolerance test is recommended starting from pubertal age. The impaired glucose tolerance may be improved by a strict diabetic diet, weight reduction where applicable, and possibly a more intensive iron chelation strategy. Insulin treatment is usually required once diabetic mellitus is diagnosed.[3]

vii) Hypoparathyroidism

Another late complication of iron overload and/or anaemia is hypocalcaemia as a result of hypoparathyroidism. This complication is less common before the age of 16[34]. The majority of patients presents with a mild form of the disease accompanied by paraesthesia. In more severe cases they may suffer from tetany, seizures or heart failure.

Oral vitamin D or its analogues may be employed to normalise serum calcium levels. In general, calcitriol, in the dosage of 0.25-1.0 μg twice daily, is sufficient to restore plasma calcium and phosphate levels to normal. Phosphate binders may be considered in cases of persistently raised serum phosphate.[3]

viii) Osteoporosis

Reduced bone mass is frequent in patients with thalassaemia. A high prevalence of osteoporosis and osteopenia has been reported[23,35]. Hypogonadism is considered the major contributing factor since sex hormones including oestrogen, progesterone and testosterone promote bone formation while the former two hormones also inhibit bone resorption. Other risk factors include hypoparathyroidism, anaemia, iron overload, ascorbate deficiency, diabetes, hypothyroidism, as well as genetic factors.[42]

Patients with osteoporosis should be given vitamin D and calcium supplements and advised to exercise actively. Dietary guidance may be employed to increase the intake of foods high in calcium. Smoking should be discouraged where applicable. Early hormonal replacement is useful to prevent bone loss induced by hormone deficiency.[42]

Bisphosphonates are potent inhibitors of bone resorption. Preliminary studies conclude that daily oral alendronate[43], intravenous zoledronic acid administered every three months[44], and monthly intravenous pamidronate[45] are effective in treating β-thalassaemia associated osteoporosis. On the contrary, the efficacy of intramuscular clodronate has not been confirmed[43].

V CONCLUSIONS

Regular blood transfusions and iron-chelating treatments have greatly improved the prognosis for patients with β-thalassaemia major. Nevertheless, due to poor compliance, many patients still receive ineffective chelating therapy and develop iron-induced complications. Thus, patient education on the therapies they receive and regular monitoring are essential to ensure that patients with β-thalassaemia major obtain optimal treatments, so as to reduce morbidity and mortality, along with improvements in the quality of life.

Table 1. Incidence rates of growth related complications

	Italian working group[34] (n=1861)	Li, C.K. et al.[8] (n=232)	Shamshirsaz A.A. et al.[35] (n=220)	Borgna-Pignatti et al.[7] (n=1146)
	Incidence rate (%)			
Failure of puberty	~ 50	38.4	17.5	55
Primary amenorrhoea	-	27.1	32.8	-
Secondary amenorrhoea	23	8.5	7.7	-
Diabetes mellitus	4.9	8.6	8.7	5.4
Hypothyroidism	6.2	6.9	7.7	11.6
Hypoparathyroidism	3.6	3.4	7.6	-

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Questions for Pharmacy Central Continuing Education Committee Program

1. Which of the following statements regarding thalassaemia is false?

A. Thalassaemia is a kind of anaemia caused by the defective synthesis of globin chains.
B. Heterozygous β-thalassaemia is usually asymptomatic and does not require drug treatment.
C. Both α- and β-thalassaemias were first found in the Middle East and South East Asia.
D. Regular blood transfusions and iron chelation therapy are the mainstays of treatment of β-thalassaemia major nowadays.
E. Precipitation of excess α-chains in both red cell precursors and mature red cells causes severe anaemia in β-thalassaemia major.

2. Which of the followings is not a consequence of untreated β-thalassaemia major?

A. Hypersplenism
B. Bony deformity
C. Growth retardation
D. Yellow skin and eyes
E. Increased chance of infections

3. Which of the following statements concerning splenectomy in thalassaemia is false?

A. It helps to reduce blood transfusion frequency as well as transfusional iron overload.
B. It must be avoided in children under the age of five.
C. Influenza virus vaccine is useful in prophylaxis of infections after splenectomy.
D. Penicillin, amoxicillin or erythromycin may be prescribed to reduce the risks of infections after splenectomy.
E. Patients with recurrent infections or bleeding may benefit from splenectomy.

4. Which of the following statements concerning deferrioxamine is true?

A. In vivo, one deferrrioxamine atom binds to one iron atom to form ferrioxamine.

2 CE Units

β-thalassaemia Major and Iron Overload

B. It binds to iron released from the breakdown of red blood cells as well as that from the liver.
C. It should be started once the patient is diagnosed with β-thalassaemia and has started receiving blood transfusions.
D. Subcutaneous injection of it is as effective as slow subcutaneous infusion in reducing cardiac complications.
E. The use of vitamin C can increase iron removal by desferrioxamine as it reduces Fe^{2+} to the more easily chelated Fe^{3+}.

5. The following factors would increase the efficacy of desferrioxamine except:

A. Early initiation of desferrioxamine.
B. The use of vitamin C 30 minutes to 1 hour after the start of desferrioxamine infusion.
C. Increasing the frequency of blood transfusions.
D. Reinforcing the patients' compliance to long-term subcutaneous infusion of desferrioxamine.
E. Converting to continuous infusion of desferrioxamine in high-risk patients with cardiac complications.

6. Which of the parameters below is the most accurate to determine body iron burden?

A. Serum ferritin level
B. Urinary iron excretion
C. Transfusional iron load
D. Liver iron concentration
E. Iron deposition in the heart

7. Which of the following statements concerning deferiprone is false?

A. It is the first oral iron-chelating agent.
B. It is used as a second line therapy for patients contraindicated or those intolerant to desferrioxamine.
C. Arthralgias are the most serious adverse effects causing discontinuation of deferiprone.
D. Deferiprone was shown to have greater cardioprotective effects than desferrioxamine as it has higher cell penetration to chelate iron from the heart.
E. In theory, three molecules of deferiprone are required to bind to one iron atom.

8. Which of the following drugs is not commonly used to treat complications of iron overload in β-thalassaemia major?

A. Angiotensin-converting enzyme inhibitors
B. Sulphonylureas
C. Oral estrogen-progesterone
D. Thyroxine
E. Diuretics

9. The following complications are common after the age of ten except:

A. hypothyroidism
B. hypersplenism
C. diabetes mellitus
D. hypoparathyroidism
E. amenorrhoea

10. Which of the following statements concerning osteoporosis in β-thalassaemia major is false?

A. Some bisphosphonates may be useful in the treatment of β-thalassaemia induced osteoporosis.
B. Genetic factor is a major contributing cause.
C. Vitamin D and calcium supplements are beneficial in its treatment.
D. Early hormonal replacement is appropriate in hormonal deficiency-induced bone loss.
E. Smoking is a risk factor of accelerated osteoporosis and should be discouraged in patients.

Answers will be released in the next issue of HKPJ.

Answers for the past issue (Jan-Mar2005)

Vol 14 No 1 - Peritoneal Dialysis: Principles and Related Practical Issues
1) D 2) C 3) E 4) B 5) C 6) D 7) D 8) A 9) C 10) E

Pure Enantiomer Drugs: Is Purer the Better?

Yung, KM; Cheng, ML

Isomerism is a phenomenon first recognized by a Swedish chemist, Jons Jacob Berzelius in 1830. It is the existence of more than one substance with identical chemical molecular formula but with different configurations, differing only in the arrangement of their component atoms.[1]

Isomerism is grossly classified into constitutional (structural) isomers and stereoisomers. Constitutional isomers are compounds with the same molecular formula but different in binding; whilst stereoisomers are substances with the same atoms bonded in the same way but different in their three-dimensional structures. Stereoisomers can further be classified into geometric isomers, which are often the result of rigidity in the molecular structure; and optical isomers, also known as enantiomers, which occur in mirror pairs. The two enantiomers are not the same in terms of their three-dimensional configurations. In the following discussion, enantiomers will be our focus. They possess an important feature of optical activity which is their ability to rotate polarized light. In order to differentiate the two enantiomers of a mirror pair, they are usually termed as S-enantiomer and R-enantiomer based on the three-dimensional configuration; or levorotatory and dextrorotatory according to their optical activity. A racemate is defined as a mixture of the two enantiomers in equal proportion.

Isomerism is common in organic chemistry and as drugs are mostly organic in nature, a number of drugs exhibit isomerism. In the past, most drugs are synthesized in the laboratory and the resulting products are mostly racemates rather than in the form of a pure enantiomer. With advancing technology, large-scale production of pure enantiomers is now feasible. In the following discussion, we shall look into some of the enantiomer pairs currently available on the market and demonstrate whether the new comers have superior efficacy over their preceding racemates.

I OMEPRAZOLE AND ESOMEPRAZOLE

Proton pump inhibitors (PPIs) represent a major breakthrough in the management of gastric acid-related disorders such as peptic ulcer, duodenal ulcer, gastritis and gastro-esophageal reflux disorder (GERD). PPIs act on the gastric H^+/K^+-ATPase enzymes (proton pumps) on the gastric parietal cells of the acid secretory canaliculus and inhibit the release of gastric acid into the gastric contents.[2] Under normal physiological conditions, gastric acid secretion is regulated by three chemical mediators; namely histamine, gastrin and acetylcholine. PPIs show their superior efficacy in acid suppression over anticholinergics, prostaglandin analogues and H_2-receptor antagonists by blocking the final step of gastric acid secretion, on which all stimulatory pathways converge. Therefore, PPIs are more effective than the older-generation acid suppressing agents in the management of acid-related disease.[3,4,5]

Omeprazole is the first PPI launched in the market which is a racemate of the S- and R-enantiomers[6]. Recently, the S-enantiomer of omeprazole was marketed in its own pure form as esomeprazole.

In the last decade, many studies have been done to compare the efficacies among omeprazole, esomeprazole (S-enantiomer) and the R-enantiomer. It was shown that, esomeprazole attained a higher plasma level than omeprazole after oral administration of comparable doses. To explain for such phenomenon, it was found that the constituting enantiomers of omeprazole are mostly metabolized by the cytochrome P450 (CYP) pathways, mainly the CYP2C19 and CYP3A4 enzymes; however, the CYP2C19 pathway is more favoured by esomeprazole over CYP3A4; and as the role of CYP3A4 is more dominant in the first-pass metabolism over CYP2C19[7], esomeprazole is subjected to less extensive first-pass effect when compared with omeprazole as a whole. This reduction in intrinsic clearance results in a higher plasma concentration area-under-the-curve (AUC) of esomeprazole compared with equal dose of omeprazole and the difference can be up to three to four times at comparable doses.

As the acid-suppressant effect of PPIs is related to the plasma AUC of active substance, the three to four-fold difference in AUC of active enantiomer translates into an increase in efficacy of esomeprazole over omeprazole at comparable doses[8] and thus results in a better 24-hour gastric pH control when esomeprazole is used.

Furthermore, esomeprazole demonstrates superiority over omeprazole in terms of inter-individual variability as the metabolism of esomeprazole is more predictable than omeprazole. This phenomenon is again explained by the difference in the metabolic pathways of esomeprazole and the R-enantiomer. As esomeprazole is mostly metabolized by the CYP2C19 pathway, it is less vulnerable to the effect of the existence of CYP450 poor metabolisers.[9]

Clinical studies comparing esomeprazole and omeprazole demonstrated that the efficacy of esomeprazole was at least comparable to that of omeprazole at licensed dosage. Study has shown that the healing rate of erosive esophagitis would improve if the intragastric pH could be maintained at 4 or above for a longer period.[10] In randomized clinical trials, treatment with standard dose of esomeprazole (40 mg/day) provided significantly greater acid control and maintained intragastric pH at above 4.0 for more than 12 hours in a greater proportion of patients than the standard doses of lansoprazole (30 mg), omeprazole (20 mg), pantoprazole (40 mg), or rabeprazole (20 mg) after 5 days of treatment[11]. In two randomized trials, healing rate was significantly higher and symptom resolution was more rapid with esomeprazole 40 mg compared with omeprazole 20 mg after treatment for up to 8 weeks in patients with erosive GERD[12,13].

Esomeprazole is as effective as omeprazole as part of the triple therapy for *Helicobacter pylori* eradication in duodenal ulcer. In two randomized, double-blind, multi-centred trials, a 7-day regimen of twice-daily esomeprazole plus amoxicillin and clarithromycin was as effective as

omeprazole-based regimens in curing *H. pylori* infection, with eradication rates of over 86% in all intention-to-treat groups.[14,15]

From the safety perspective, esomeprazole is generally well tolerated and its side effect profile does not differ significantly from that of omeprazole. Like omeprazole, esomeprazole may inhibit CYP2C19 pathway;[16] thus, possible drug interactions should be monitored when esomeprazole is used concurrently with CYP2C19 substrates such as phenytoin, cyclophosphamide and tricyclic antidepressants such as imipramine.

Although published literature appears to suggest the superiority of esomeprazole to omeprazole, the study results should be interpreted with caution as the doses of PPIs used in the trials may not be comparable. In general, we agree that PPIs exhibit a class effect and thus they are interchangeable in most circumstances.

II CITALOPRAM AND ESCITALOPRAM

Citalopram is a selective serotonin reuptake inhibitor (SSRIs) antidepressant, which inhibits the reuptake of serotonin at ganglionic synapses of the brain. It has been proven to be effective in the management of major depression in the general population, elderly and those patients whose depression is associated with anxiety. Citalopram has also been shown to be effective in the management of panic disorder and obsessive compulsive disorder.[17]

Citalopram, like other SSRIs, has been frequently compared with the older-generation antidepressants such as tricyclic antidepressants; head-to-head comparisons showed that citalopram has a lower potential for drug interactions and is better tolerated even in the elderly population, thus it is more suitable for use in the elderly than the tricyclics.[18] Side effects associated with citalopram are usually mild to moderate, which include nausea, vomiting, increased sweating, headache, dry mouth, tremor, sedation and insomnia[19] and it rarely causes stimulation. In addition, citalopram can be prescribed to patients with renal and hepatic dysfunction with appropriate dosage adjustments. Among all SSRIs available on the market, citalopram is the most selective inhibitor for serotonin reuptake.[17]

Citalopram and its metabolites are racemate with escitalopram being its S-enantiomer. Escitalopram is the pharmacologically active moiety in relation to inhibition of serotonin reuptake, and it accounts for 24% to 49% of the total plasma citalopram level; on the other hand, the R-enantiomer of citalopram appears to be pharmacologically inactive in earlier findings. However, if the belief that the R-enantiomer was an inactive moiety had been true, the efficacy of escitalopram would have been comparable to citalopram at a dose that was twice as much as that of escitalopram; however, this was not demonstrated in studies on the management of major depressive disorder.[20] Further research on the difference between the two enantiomers showed that the R-enantiomer might actually counteract the activity of escitalopram. In animal studies, both escitalopram and citalopram increased the level of extracellular serotonin with escitalopram being more potent. However, when the escitalopram was co-administered with the R-enantiomer of citalopram, the latter inhibited the activity of escitalopram in a dose-dependent manner.[20] Therefore, the presence of R-enantiomer in citalopram may reduce the efficacy of escitalopram. Clinically, escitalopram has been shown to be slightly superior to citalopram in terms of efficacy, especially with respect to the onset of action.[20]

In short, both escitalopram and citalopram are efficacious and well-tolerated. In terms of efficacy and onset of action, escitalopram may be superior to citalopram. The potential benefit achieved with escitalopram should however be balanced against the extra drug cost.

III OFLOXACIN AND LEVOFLOXACIN

Levofloxacin is the levorotatory-enantiomer of the racemate ofloxacin. Ofloxacin and levofloxacin are fluoroquinolone antibiotics which act by inhibiting bacterial DNA gyrase, a type II topoisomerase that is essential for bacterial DNA replication and transcription. Levofloxacin was approved by the Food and Drug Administration of the United States in 1996 for the treatment of community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, acute maxillary sinusitis, uncomplicated skin and skin structure infections, acute pyelonephritis, and complicated urinary tract infections due to susceptible organisms.

Both ofloxacin and levofloxacin have good coverage against gram-negative bacteria such as *Escherichia coli, Klebsiella sp, Enterobacter sp, Proteus sp, Salmonella sp, Shigella sp* and *Campylobacter sp*. For gram-positive bacteria, both of them again share a similar spectrum of activity, which are only limited to methicillin-sensitive staphylococci and some streptococci.[21] Despite the similarity in the activity spectrum, their potencies against bacteria may differentiate one from the other. Based on the MIC90s of ofloxacin and levofloxacin, the activity of levofloxacin is generally twice of, or at least similar to, that of ofloxacin.[22,23] In addition, although levofloxacin only has modest *in vitro* activity against anaerobic bacteria, its ability to inhibit anaerobic bacteria is greater than that of ofloxacin in general.[22] Levofloxacin also exhibits post-antibiotic effect (PAE) against test strains of *E. coli* which is similar to PAE for ofloxacin.[24]

Similar to ofloxacin, the oral bioavailability of levofloxacin is high, approaching approximately 99%.[25] Therefore, in patients with functional gastrointestinal tracts and without contraindications, intravenous and oral routes are considered interchangeable. The pharmacokinetics of levofloxacin is similar when it is administered as once-daily regimen and multiple-daily regimen. This property allows levofloxacin to be dosed once daily, as opposed to ofloxacin, which is usually dosed twice daily. However, the reason behind the difference in dosing regimen remains to be elucidated.

Both levofloxacin and ofloxacin are well tolerated and their safety profiles are similar. From the results of clinical trials, levofloxacin showed lower overall frequency of gastrointestinal and central nervous system adverse events compared with ofloxacin.[24]

IV CETIRIZINE AND LEVOCETIRIZINE

Levocetirizine is the levorotatory-enantiomer of cetirizine. Cetirizine, a racemate of levocetirizine and dextrocetirizine, is a second-generation antihistamine indicated for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria.[26] Levocetirizine has been recognized as the active enantiomer of cetirizine. Both cetirizine and levocetirizine cause minimal sedation and anticholinergic side effects (e.g.

dry mouth) when compared with the older-generation antihistamines.[27] The use of cetirizine within normal dosage range is not associated with cardiac adverse effects, contrary to terfenadine and astemizole.

In clinical studies comparing the efficacies of cetirizine and levocetirizine in terms of inhibition of histamine-induced allergic symptoms, neither of them showed superiority over the other at equivalent doses. In addition, levocetirizine fails to demonstrate a superior side effect profile to cetirizine.[28] Thus, the use of levocetirizine does not appear to be associated with extra clinical benefit to patient and selection between the two drugs should probably be based on non-clinical factors such as acquisition costs.

V CONCLUSION

As discussed above, a number of products in the form of pure enantiomers have been marketed in recent years, after the introduction of its racemate products. The introduction of pure enantiomers may be a genuine improvement in efficacy over the racemate, or could merely be a marketing strategy of the drug company. Healthcare professionals should exercise prudence in the process of drug selection.

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Design and Synthesis of Adefovir Dipivoxil: a Nucleoside Analogue for the Treatment of Hepatitis B Viral Infection

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Hepatitis B is a necroinflammatory disease of liver due to the infection of an Orthohepdna virus. Chronically infected with hepatitis B virus (HBV) may lead to the development of cirrhosis and carcinoma in liver. Nucleoside analogues, which mimic natural nucleoside, can be competitively incorporated into newly synthesized DNAs and cause chain termination of replication in HBV; thus stop their proliferation. In this review article, the chemical synthesis and clinical applications of an analogue compound of nucleosides, namely adefovir dipivoxil is described. This antiviral agent is a diester prodrug of adefovir and has been approved by FDA for effective treatment of HBV infection.

I INTRODUCTION

Hepatitis is an inflammatory disease of the liver characterized by diffuse or patchy hepatocellulas necrosis and may be acute or chronic. It is an epidemic disease due to the inflection of hepatitis virus. It is a global health problem; today more than 400 million people worldwide carry the virus[1,2]. Hepatitis B (HB) is the prototype virus of the hepadnaviridae, a group of animal viruses that signifies the hepatotropism and particular DNA replication of viral genome as well as production of excess surface antigen particles. Hepadnaviridae is consist of 2 genera; namely the *Orthohepadnavirus* genus that infects mammals and primates, such as HBV[3] and the *Avihepadnavirus* genus that infects birds, such as DHBV[4,5].

II STRUCTURE OF Hep B VIRUS

The outer envelope of the infectious virion consists of Hep B surface antigen. Within the core is the partially double-stranded DNA which consists 4 open reading frames encoding the relevant viral proteins as illustrated in Figure 1.

III REPLICATION OF Hep B VIRUS

When virus attaches to the appropriate hepatocyte receptor, it becomes internalized and uncoated in the cytosol. Genome of the viron translocates to the nucleus where it is converted into a double-stranded covalently closed circular DNA (cccDNA) molecule, to serve as the template for the synthesis of viral transcript by host RNA polymerase II. One of the viral RNA transcripts known as pregenomic RNA (pgRNA) forms the template for (-)DNA strand synthesis. It also constitutes the message for polymerase protein translation. Polymerase has 3 functional domains; a terminal protein (involve in DNA priming), a reverse transcriptase and a RNase H involved in pgRNA degradation. The viral polymerase binds to ε (a secondary RNA structure at the 5' end of the pgRNA) and directs the synthesis of a short primer using as template the nucleotide sequence of the bulge. The polymerase-primer complex translocates to the 3' end of the pgRNA and base-pairs with direct repeat 1 (DR1). As the complex proceeds towards the 5' end of the pgRNA, the (-)-DNA strand is synthesized by RT and the RNA template is concurrently degraded by the RNase H activity of the polymerase, except for the final 18 bases. These bases constitute the RNA primer which initiates (+)-DNA strand synthesis. The primer hybridizes with the DR1 region at the 5' end of the newly synthesized (-)-DNA stand and anneals with the homologous DR2 regions. (+)-DNA strand synthesis then proceeds in the direction shown by the arrow[6].

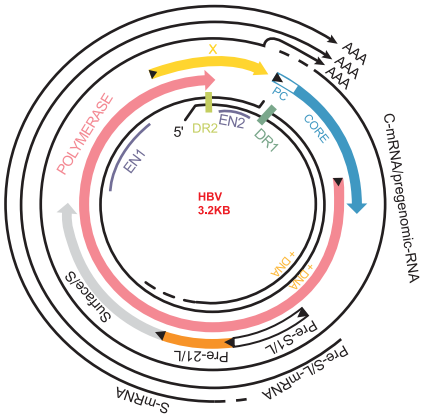

Figure 1. Genomic organization of the hepatitis B virus showing the partially double-stranded DNA and the positions of the direct repeats (DR) 1 and 2, and those of enhancers 1 and 2 (EN). Also shown are the four open reading frames encoding the relevant viral proteins as indicated, as well as the various RNA transcripts terminating at a common polyadenylation signal[6].

IV APPROACHES OF Hep B TREATMENT WITH NUCLEOSIDE ANALOGUES

The agents currently available for the treatment of the chronic HBV infection are divided into 2 main groups: immunomodulators and nucleoside analogues[6]. At present, only IFN-α, lamivudine and adefovir dipivoxil are approved for the treatment of chronic HBV[7]. Immunomodulators act by promoting cytotoxic T cell activity for lysis of infected hepatocytes and by stimulating cytotoxic production for control of viral replication. Nucleoside analogues on the other hand act by suppressing HBV replication at the level of DNA synthesis, and in addition there is evidence that they may enhance immune clearance of infected hepatocytes.

Adefovir dipivoxil (AD, Hepsera®, Gilead Sciences, Inc.) is a nucleoside analogue that inhibits wild-type hepatitis B virus and lamivudine-resistant HBV mutants *in vitro* and *in vivo*[8-10]. The chemical formula of adefovir dipivoxil is bis-POM-PMEA or 9-[2-[bis(pivaloyloxy)methoxyl]phosphinyl]methoxyethyl adenine. It is a diester of adefovir (PMEA) and has a molecular formula of $C_{20}H_{32}N_5O_8P$; a molecular weight of 501.48 and a white to off-white crystalline powder with an aqueous solubility of 19 mg/ml at pH 2.0 and 0.4 mg/ml at pH 7.2. It is a chemically synthesized prodrug that is able to mimic natural nucleosides[11,12]. The structure formula of this prodrug is shown in Figure 2.

Stages in the life cycle of HBV that could be inhibited by nucleoside analogues include the synthesis of the (-)-DNA strand, the amplification and the replenishment of the cccDNA formation in newly infected cells[13,14]. As Figure 3 illustrated, nucleoside analogues could be incorporated into newly synthesized HBV-DNA causing chain termination, and thus inhibiting viral replication. In addition, some of them competitively inhibit the DNA-dependent and reverse transcriptase activity of the viral polymerase.

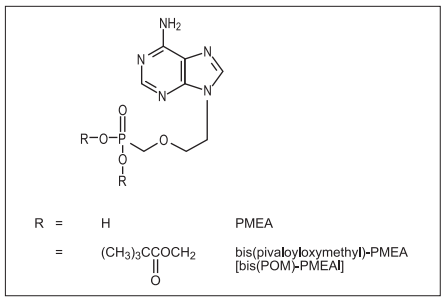

Figure 2. Structural formula of PMEA and bis-POM-PMEA[12].

V CHEMICAL SYNTHESIS OF AD

Several methods have been developed for the synthesis of adefovir intermediates (B2-01). The main focus of these methods is to either to prepare the carbon-nitrogen or carbon-oxygen bonds in the chain of (B2-01) via alkylation reactions. Then compound (B2-02) can be prepared from the hydrolysis of phosphonate diester and coupled to chloride (B2-03) to give the final product (Figure 4). Although the complete chemical synthesis of AD involves several steps, it could be divided into several parts. Firstly, it is the synthesis of diethyl-PMEA. Secondly, the synthesis of PMEA and thirdly, the synthesis of bis-POM-PMEA (AD)[15] and finally, crystallization and purification of AD.

i) Methods for Diethyl-PMEA Synthesis[16,17]

In a reactor under an inert atmosphere, e.g., nitrogen, mixture of diethylphosphite, paraformaldehyde, and triethylamine in toluene (15: 4: 1: 50 ratio respectively) is prepared and heated to 87°C for 2 hours with agitation. Then the heated mixture is maintained at reflux for another 1 hour until the reaction is complete. Completion of the reaction could be determined by TLC until trace or no detectable diethyl phosphite is found and confirmed by ^{1}H-NMR showing no more than 1% of the diethyl phosphite peak at 8.4-8.6 ppm.

Then, the solution is cooled to about 1°C and *p*-toluenesulfonyl chloride is added, followed by slowly adding of triethylamine (ratio is 5:4) at a temperature not higher than 10°C over 3-6 hours in an exothermic reaction mode. The resulting mixture is warmed to 22°C and stirred for at least 5 hours until the reaction is complete. Reaction completion is again monitored by TLC (trace or no *p*-toluenesulfonyl chloride detectable) and confirmed by ^{1}H-NMR (*p*-toluenesulfonyl chloride doublet at 87.9 ppm no longer detected).

Finally, the solids are removed by filtration and rinsed with toluene. The combined washings and filtrate are washed either twice with water, or optionally with a sequence of water, 5% aqueous sodium carbonate (10 times as the weight of solids), and twice with water. In the event emulsion occurs, brine may be added to the first organic/water mixture.

ii) Methods for PMEA Synthesis[16,17]

Same as the above synthesis, PMEA also produced in a reactor having an inert atmosphere. A mixture of diethyl PMEA, acetonitrile, and bromotrimethylsilane (in 2: 4: 3 ratio) is heated to and maintained at reflux for about 1-3 hours with agitation, until the reaction is complete. Reaction completion is monitored by 31p NMR or HPLC (no diethyl PMEA and no more than 2% monoethyl PMEA detected).

The solution is then distilled at 80°C in vacuum to a semi-solid, which is taken up in water and warmed to about 55°C for about 30-60 minutes with agitation to dissolve all solids. The resulting mixture is cooled to about 22°C, adjusted to pH 3.2 with aqueous sodium hydroxide, the contents are heated to about 75°C until the consistency thins (about 15-120 minutes), cooled to about 3°C, and stirred for at least 3 hours (3-6 hours).

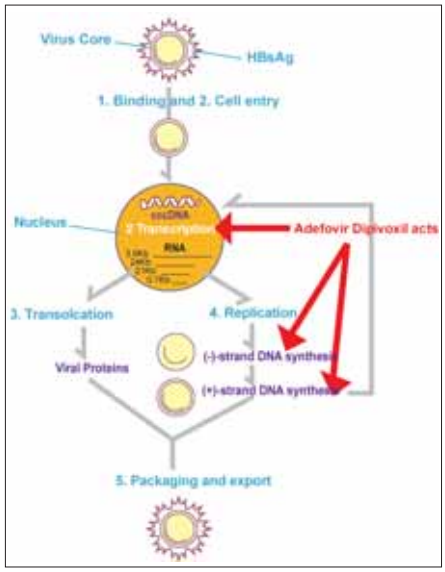

Figure 3. Action sites of AD.

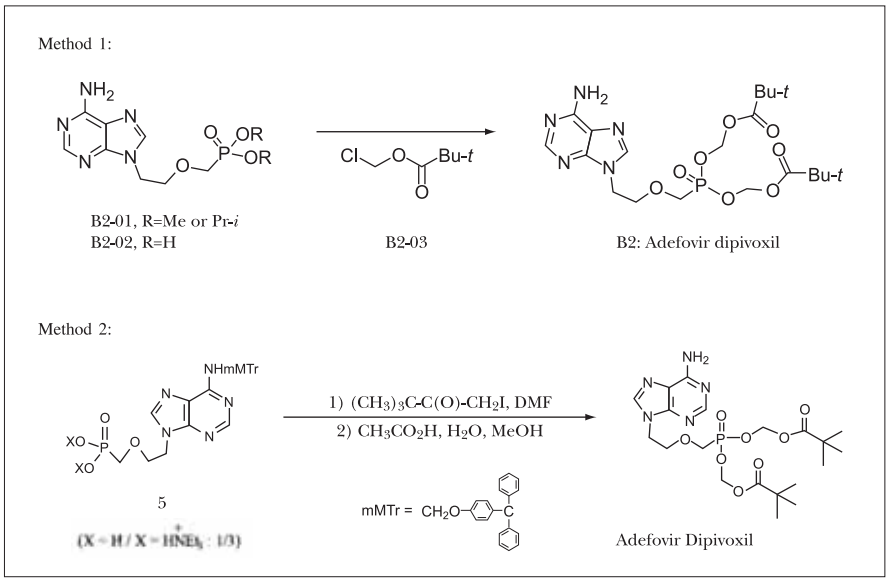

Figure 4. Methods of chemical synthesis of adefovir dipivoxil (AD)[15].

Furthermore, the slurry is filtered and the filter cake is rinsed with water. The wet cake is suspended in water (3 times more than the previous step) and the suspension is heated to about 75°C with vigorous stirring. After stirring for about 2 hours, the slurry is cooled to about 3°C and stirred for at least another 2 hours. The slurry is filtered and the filter cake is rinsed sequentially with two portions of water and two portions of acetone. The isolated solid is dried in vacuum at no more than about 90°C to a low water content (no more than 0.5% water detected by KF titration), to provide PMEA as white crystals. The product is milled to a fine particle size.

iii) Methods for AD Synthesis[16,17]

An exemplary method to prepare AD comprises suspending 1 molar equivalent of PMEA in a volume of about 5.68-56.8 equivalents of NMP/equivalent PMEA and, after one suspends the PMEA, adding about 2-5 molar equivalents, often about 2.5-3.5, usually about 3 molar equivalents, of triethylamine ("TEA") to the solution using mild to moderate agitation. One then adds about 3-6 molar equivalents, often about 4.5-5.5 molar equi chloromethyl pivalate to obtain a reaction mixture. We usually prepare the reaction mixture at room temperature. One heats the reaction mixture to maintain a temperature of less than 66°C, typically about 28-65°C, usually between about 55-65°C for about 2-4 hours to conduct the reaction. The time needed to heat the reaction mixture to about 28-65°C is not critical and can vary depending on the reaction mixture volume and the capacity of the apparatus used to heat the mixture. Mild or moderate agitation maintains solids in suspension during the reaction and this minimizes extensive splashing of the reactants in the reaction vessel. This method results in a product comprising AD produced by the process of reacting the listed reactants, typically under the given conditions.

iv) Crystallization of AD

Nucleation rates typically increase when the degree of supersaturation and the temperature increases. Crystalline AD is prepared by allowing crystal formation in an AD composition, usually from a solution of AD in a crystallization mixture containing at least about 45% of AD and about 55% crystallization solvent. This supersaturation solution allows nucleation, which means crystal formation. The process favors at lower temperature, high solvent evaporation rate and altering solvent composition, for instance, by adding a miscible non-solvent or poor solvent. Moreover, AD is not freely soluble in some crystallization solvents; one usually uses organic solutions containing an amount of AD that is near the upper solubility limit in the crystallization solvents. The lower amount, about 6%, is the minimum amount of AD needed in a solution to consistently yield crystals. Certain solvents, for example, methanol or CH_2Cl_2, can dissolve more than 50% (w/v) AD.

VI CLINICAL APPLICATIONS AND UNDESIRABLE EFFECTS

Adefovir is an acyclic nucleoside analogue of adenosine monophosphate. Following further phosphorylation by *in vivo* cellular kinase, the compound is converted to a phosphonic acid intermediate as with other nucleoside analogs. The phosphorylated adefovir can inhibit HBV DNA polymerase (a reverse transcriptase) by competing with the natural substrate deoxyadenosine triphosphate and causing elongation process of DNA chain to termine after its incorporation into the viral DNA. The inhibition constant (Ki) for adefovir diphosphate for HBV DNA polymerase is 0.1 μM but it is a weak inhibitor to human DNA polymerase α and γ with Ki values of 1.18 μM and 0.97 μM, respectively.

Hepsera is the brand name of AD currently available in the market. Although it has been approved for curing chronic HB in adults by FDA since 2002, there were several studies documenting about the side effect of Hepsera. The most common side effects are weakness, headache, stomach pain and nausea. Serious side effects may include a severe kidney problem called nephrotoxicity, increase the chance of developing a form of HIV that cannot be treated with usual HIV and lactic acidosis and liver problems.

VII CONCLUSION

In conclusion, Adefovir Dipivoxil is a powerful nucleoside analogue for the treatment of Hep B virus[18]. However, some side effects caused by the drug are also quite undersiderable. Therefore, combination therapies involving two or more nucleoside analogues, immunomodulators or gene therapies are still preferred and certainly will be the future treatment regimens for chronic HBV infection.

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Bioactive Components in *Prunella vulgaris* L. (夏枯草) Provide Effective Protection against Liver Disturbances and Viral Infections

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Botanical Name: *Prunella vulgaris* L. (夏枯草)
Plant Family: Labiatae
Pharmacopoeia Name: Spica Prunellae
Other Names: Xiakucao, Self-heal Spike, Common Selfheal Fruit-Spike, Heal-all, Prunella, Self-heal
Names in other countries: Utsubogusa (Japan), Gewohnliche Braunellls (Germany), Prunelle commone (France)

I ABSTRACT

Prunella vulgaris L. (Xiakucao or Self-heal) has been used by the Chinese as a folk medicine for hundreds of years. The herb is collected in the summer when the spikes become brownish red and is dried in the sun. The aerial parts of the plant, especially the dried flowered fruit-spike, are useful. It is made into a tincture, an infusion, or an ointment for medicinal use. The herb has been shown to possess effective treatment for viral infection. It is particularly effective in the treatment of herpes simplex I (HSV) and human immunodeficiency diseases (HIV). The herb is also anti-bacterial and anti-inflammatory. Internally, it has been used to resolve disturbances (heat) in liver, to treat hemorrhage and to decrease excessive menstruation. Externally, it is used for minor injuries, sores, burns, bruises, sore throat, mouth inflammations and hemorrhoids. These broad pharmacological effects of the herb, therefore, have attracted a lot of interest from the public and researchers.

II DESCRIPTION AND BACKGROUND

Prunella vulgaris L. is a whole herb plant that dies off at the end of summer, so it is named Xia Ku Cao in Chinese pinyin which means the "grass which perishes at the end of summer". The plant, commonly known as Self-heal or Heal-all, belongs to the genus of *Prunella* which is a genus of the Labiatae family that is often referred as the Mint Family and which consists of 72 genera and 734 accepted taxa overall. Currently only two species of *Prunella* has been identified and they are a common weed indigenous to Europe, Asia and North America. *Prunella* grows in temperate and cool regions. It can be found in sandy soils, pastures and along roadsides or railroads, thriving in sunny waste ground[1].

Prunella is a prostrate, annual to perennial plant that grows to approximately 45 cm in height. It is a hemicryptophyte and faintly pubescent herb. The stem of this plant which is glabrous to villous on angles or antrorse strigose, is erect and rarely creeping. The angles are minutely winged and about 3 mm broad. Leaves, typically petiolate as simple, single or multiple from base, are oval to lance-shaped; mostly smooth and opposite on the angled stem. The petioles are up to 6 cm long and 2 cm broad at base of the plant but reduced lanceolate above with a few shallow teeth. They are villous and winged on upper stem. Flower of this herb is zygomorphic and crowded on a terminal head; hooded with a fringed lower lip Corolla is bilabiate and whitish-purple. Corolla tube extends up to 5 - 8 mm long in flower and it is glabrous (Figure 1). Upper lip is galeate, often purple in color, 6-7

Figure 1. Prunella vulgaris L. with fruit-spikes and fresh flower (insert).

Contraindications

No contraindication has been reported at the moment of this publication.

Undesirable Effects

No reports of side-effects or adverse reactions associated with the use of *P. vulgaris*. But safety during pregnancy and lactation is unproven. Do not use prunella if diarrhea, nausea, stomachache, or vomiting is present.

Interaction with Conventional Drugs

No interaction with conventional drugs has been reported at the moment of this publication.

mm long and 5 mm broad with a few villous hairs externally on the midvein. Lower lip is 3-lobed. Lateral lobes are 2-3 mm long and 1.5 mm broad. Central lobe is 4 mm long, deflexed, fimbriate-erose at apex and light purple in color. The flower possesses 4 stamens, which are didynamous, includes under the galea. Upper pair of the stamens is adnate near the base of galea while lower pair is adnate near the base of corolla tube. Filaments are purple, glabrous, less than 1.2 cm. Anthers are purple-brown in color. Style is inserted between upper pair of stamens, glabrous, lilac and 1.6 cm long. Calyx possessing villi on margins and on nerved, is bilabiate, accrescent and 10-nerved. Flowering time normally is from May to September. Nutlets are up to 2 mm long, brownish-yellow and glabrous.

The medicinal part of *Prunella vulgaris* L. is the aerial part of the plant, especially the dried flowered fruit-spike. It has been used exclusively in folk medicine for quenching liver-fire and counteracting inflammation of the eyes, used for inflammation of the eyes, eye pain, headache and dizziness[2]. Other than that, it was used in reducing nodulation and inducing subsidence of swelling, used for scrofula, goiter, mastitis with swelling and pain, hyperplasia of breast, and for hypertension. However, in recent years, several studies have indicated that the extracts of *P. vulgaris* also possess activities against some viral infections[3,4].

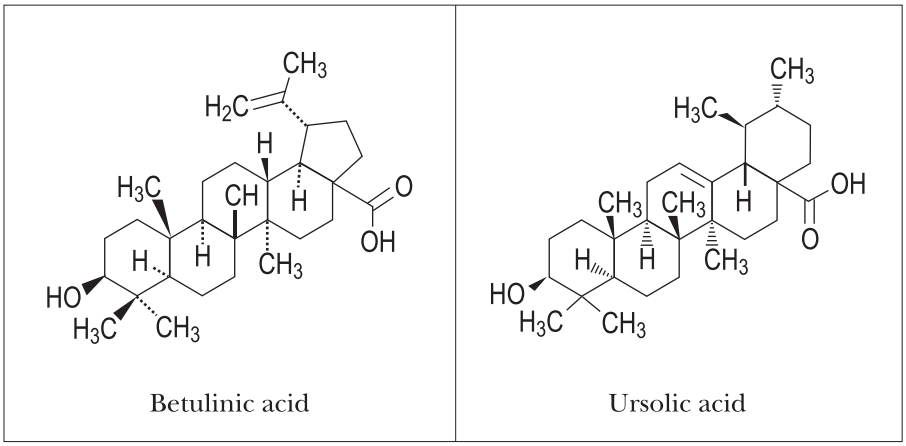

Figure 2. Chemical structures of two triterpenoids present in Prunella vulgaris L.

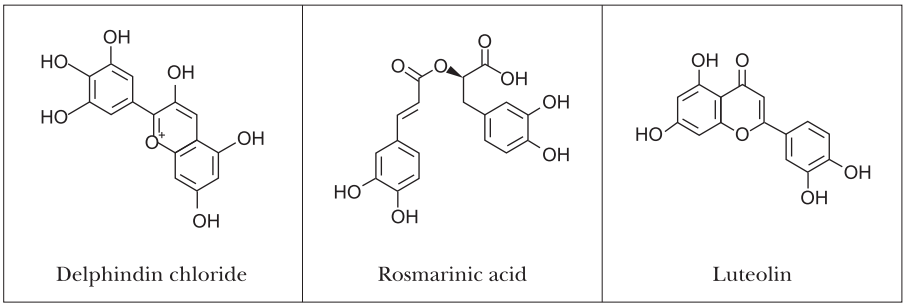

Figure 3. Chemical structures of three flavonoids isolated from Prunella vulgaris L.

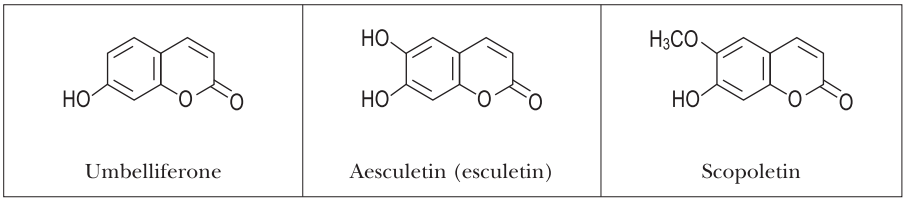

Figure 4. Chemical structures of some coumarins present in Prunella vulgaris L.

III BIOACTIVE CONSTITUENTS

P. vulgaris L. is odorless but gives a bitter and pungent taste due to some essential oil and some bitter principles[5]. Various phytochemical analyses of the herb lead to the discovery of a number of bioactive components mainly found in the aerial part of the herb, especially the dried flowered fruit-spike. These bioactive constituents include prunellin[6], triterpenoids (Figure 2), flavonoids (Figure 3), sterol glycosides and coumarins (Figure 4)[7]; all of them are suitable for medicinal applications.

Studies on some of the constituents found in the herb include the following:

i) **Prunellin**[6] **-** This was isolated by a group of researchers from the University of California, Davis in 1989. *In-vitro* studies with prunellin demonstrated that this compound could block cell-to-cell transmission of HIV. The studies showed that cells exposed to HIV in the presence of prunellin remained completely uninfected. Researchers from Lady Dais Institute for Medical Research suggested that Prunellin exerted an anti-HIV effect by preventing the virus from binding to cells. Other *in vitro* studies also indicated that prunellin inhibited the activity of reverse transcriptase because of its anionic polysaccharide chemically similar to drugs such as heparin[8].

ii) **Triterpenoids -** Triterpenoids are terpenoids derived from 30-carbon squalene and oxidosqualene precursors. These compounds are extremely common and are found in most plants and possess a wide spectrum of biological activities. At least more than half a dozen of triterpenes, namely oleanolates, betulinates, ursolates, maslinates, rutin, 2α,3α-dihydroxyurs-12-en-28-oic acid, 2α-hydroxursolate *etc* with antiviral activity against Herpes simplex virus and anti-inflammatory. They are bactericidal, fungicidal, antiviral, cytotoxic, analgesic, anticancer, spermicidal, cardiovascular, anti-allergic. Some of them are useful in medicine[9,10,11,12]. The triterpene compounds isolated from Prunella include ursolic acid, betulinic acid, 2α,3α-dyhydroxyurs-12-en-28-oic acid, 2α,3α-24-trihydroxyrus-12,20(30)-dien-28-oic acid, 2α,3α,24-trihydroxyolean-12-en-28-oic acid, 2α,3α,24-trihydroxyolean-11,13(18)-dien-28-oic acid, (12R,13S)-2α,3α,24-trihydroxy-12,13cyclotaraxer-14-en-28-oic acid, (13S, 14R)-2α,3α,24-hydroxy-13,14-cyclooolean-11-en-28-oic acid, and 2α,3α-dihydroxyursolic acid. Monotrpenes, such as d-camphor and d-fenchone are also found in the herb[13].

iii) **Flavonoids -** These are an ubiquitous group of polyphenolic substances which are present in most plants, concentrated in seeds, fruit skin or peel, bark, and flowers. A great number of plant medicines contain flavonoids, which have been reported by many authors as having antibacterial, anti-inflammatory, antiallergic, antimutagenic, antiviral, antineoplastic, anti-thrombotic, and vasodilatory actions. The structural components common to these molecules include two benzene rings on either side of 3-carbon ring. Multiple combinations of hydroxyl groups, sugars, oxygens, and methyl groups attached to these structures create the various classes of flavonoids, namely flavanols, flavanones, flavones, flavan-3-ols (catechins), anthocyanins, and isoflavones[14]. Flavonoids have been shown in a number of studies to be

potent antioxidants, capable of scavenging hydroxyl radicals, superoxide anions, and lipid peroxy radicals. The flavonoids found in the herb are delphinidin, cyanidine, rosmarinic acid, luteolin, homoorientin (isoorientin) and cinaroside.

iv) **Sterol glycosides -** These molecules are synthesized in plants; whereas animals obtain them through their diet. Many epidemiological studies of groups consuming diets rich in vegetables and fruits have indicated a reduced incidence of various types of cancer, cardiovascular disease, diabetes, and other chronic disease[15]. Sterol glycosides include β-sitosterol-β-D-glucoside, stigmasterol-V-D-glucoside, stigmast-7-en-3 β-D-glucoside and spinasterol-β-D-glucoside.

v) **Conumarins -** Coumarins belong to a group compounds known as the benzopyrones, all of which consists of a benzene ring joined to a pyrone. Within a plant, although coumarins are mainly synthesized in the leaves, they occur at the highest levels in the fruits, followed by the roots and stems. In addition, seasonal changes and environmental conditions may affect the occurrence in various parts of the plant. Coumarins have a variety of bioactivities including anticoagulant, estrogenic, dermal photosensitizing, antimicrobial, vasodilator, molluscacidal, antithelmintic, sedative and hypnotic, analgesic and hypothermic activity[16,17]. Coumarins isolated from Prunella include umbelliferone, aesculetin (esculetin) and scopoletin.

IV CONTEMPORARY USES

P. vulgaris L. is traditionally used for treatment of: **i)** bloodshot eyes due to disturbances of liver (liver-fire), usually with Flos Chrysanthemi, Herbal Taraxaci, *etc.*; **ii)** for painful sensation of the swollen eye-ball that is more severe at night, with the powder form of Rhizoma Cyperi 30 g, Radix Glycyrrhizae 6 g, and 6 g taken twice a day; **iii)** for painful sensation of eye-balls due to deficiency of the liver-Yin, with Radix Angelicae sinensis, Radix Paeoniae alba, *etc.*; **iv)** for the syndrome of hyperactivity of liver-Yang of flare-up of liver-fire (manifested as red, painful, swollen and watery eyes, headache and dizziness), restlessness and insomnia, it may be used singly or combined with drugs like *Chrysanthemi indici* (野菊花), *Concha haliotidis* (石决明), Radix Scutellariae (黄岑), etc. All of the above are collectively known as the "Reducing Liver-fire to brighten vision" function of *P. vulgaris*.

Besides, it is used for **v)** treatment of Scrofula, goiter, mastitis, mumps, *etc.* due to accumulation and retention of evil factor as phlegm-file (manifested as scronfula, lipoma, swollen glands or goiter), it may be used as a single medicine for preparation of soft extract taken for a duration of time, or combined with Radix Scrophulariae (玄参), Bulbus *Fritillariae thunbergii* (浙貝母) *etc.*, which may be selected according to the syndrome of the specific patient.

Modern preparations of the herb are now available in the market as a tincture for external use to cure wounds; and in tablet, syrup, or capsule forms for internal use as an astringent in treating inflammation of the eye, eye pain at night, headache and dizziness; scrofula, goiter, mastitis with swelling and pain, hyperplasia of breast, hypertension, liver weakness, diarrhea, and sore throat.

V MODE OF ACTION

i) Hypotensive effect

P. vulgaris decoction was proved to reduce high blood pressure in animals. A water decoction and 30% alcohol solution decoction of *P. vulgaris* have been found to lower cholesterol level and decrease blood pressure in laboratory narcotic animal experiments. The decoction of the herb administered intravenously to dogs at 100 mg/kg produced a marked hypotensive effect and also tachyphylaxis. Intravenous administration of 1-1.5 g of the decoction to dogs reduced blood pressure by 40-60 mm Hg, which was readily restored to the original levels in 2-5 minutes. Intraperitoneal dosages of 3-4 g decreased the blood pressure by 30-40 mm Hg in 15-30 minutes; the effect lasted for 1-2 h. Oral administration of 2-5 g caused in 30-60 minutes mild hypotension lasting for 2 hours. The hypotensive action was attenuated by vagotomy. In heart perfusion experiments with toad heart and rabbit heart, low concentration decoction of *P. vulgaris* caused exiting and caused swing in the heart rate to increase while higher concentrations had the opposite effect[18].

ii) Good Diuretic Effect

P. vulgaris is rich in potassium. It could be used as good diuretic. A decoction of *P. vulgaris* showing a diuretic effect, caused the rabbit uterus to shrink strongly and made rabbit gut wriggle strongly[19].

iii) Antibacterial Effect

P. vulgaris decoctions after properly diluted in tubes have been proved a strong inhibitor to diarrheae bacilli. A dilution at 1:640 showed strong control of tuberculin. A few studies reported that the decoction of *P. vulgaris* inhibited many bacteria, such as diarrhea, *Salmonella typhi, Vibrio cholerae, E. coli, Proteus mirabilis, Staphylococcus aureus* and *Mycobacterium tuberculosis*[20,21,22]. The alcohol decoction of *P. vulgaris* also showed inhibition on *Pseudomonas aeruginosa* while a water decoction of *P. vulgaris* was inhibitory to fungi in test tubes[20].

iv) Effect on Cardiac Muscle

Low dosages have an exciting action and cause heart heat swings to increase but high dosages make swings decrease and show an inhibiting effect[19].

v) Effect on Smooth Muscle

A 50% decoction of Prunella caused prominent and prolonged tonic concentrations of the isolated uterus of nonpregnant rabbits. These effects on the pregnant uterus, however, were weak. The decoction increased rhythmic peristalsis of the isolated rabbit intestine; the duodenum was especially sensitive to it while the ilea response was weak[18].

vi) Anti-inflammatory Effect

P. vulgaris showed a good anti-inflammatory effect[5]; The effect derives from and is related to the synthesis and higher secretion rates of adrenocortical hormones, especially of the glucocorticoid (GCS). Besides, one of the triterpenoid compounds, 2α,3α-dihydroxyursolic acid, found in *P. vulgaris* had been demonstrated to significantly inhibit the release of β-hexosaminidase from RBL-2H3 cells in a dose-dependent manners; the IC_{50} value was found to be 57 μM. When the isolated compounds were tested for their effects on the production of nitric oxide from cultured murine macrophage, RAW 264.7 cells, ursolic acid and 2α-hydroxyursolic acid exhibited strong inhibitory activities (IC_{50} values, 17 and 27 μM, respectively)[12].

vii) Function as Immuno-suppressor

The injection of *P. vulgaris* could make thymus gland and spleen atrophy, increase the size of the adrenal gland, also make the level of hydrocortisone (cortisol) increase to a high level. All these indicate that *P. vulgaris* is a good natural immuno-suppressor[23].

viii) Effect on HIV and Herpes simplex viral diseases

Scientific study has shown prunella an effective herb for treatment of viral infections. Prunellin, an anionic polysaccharide isolated from prunella had been shown to significantly inhibit HIV-1 replication with very low toxicity[6]. The extracted inhibit the proliferation of HIV-1 in both lymph and blood. Although prunellin was unable to prevent HIV-1 infection when cells were pretreated with the purified herbal extract, the virus' ability to cause infection was dramatically decreased when it was saturated with prunellin. The purified extract was also able to block cell-to-cell transmission of

HIV-1. Moreover, the extract was also able to interfere with the ability of HIV-1 and purified gp120 to bind to CD4 cells. The researchers suggested that the purified extract antagonizes HIV-1 infection of susceptible cells by preventing viral attachment to the CD4 receptor[24,25] or by inhibiting HIV-1 entry by disrupting the formation of gp41 six-helix bundles[26].

Besides, a study of 472 Chinese medicinal plants found that prunella was among the ten most effective in the treatment of herpes simplex I[27]. A bioactive component, which is a polysaccharide in the herb, was shown to be responsible for downregulation of the expression of herpes simplex virus 1 and 2 infection (Figure 5) and it has a different mode of anti-HSV action from acyclovir[3].

VI CONTRAINDICATIONS

P. vulgaris should be used with caution in cases with a weak stomach and spleen. Long term usage can cause irritation for the stomach. If long term usage is necessary, add dang shen (當參) (dried root of *Codonopsis pilosula*) and bai zhu (白朮) (dried rhizome of *Atractylodes macrocephala* Koidz to the formulae being used. In addition, this herb is generally thought to be safe when taken internally in the recommended amount, but safety during pregnancy and lactation is as yet unproven so should be avoided. Patients with high blood pressure or hear disease should consult with their health care professional before taking prunella supplements.

VII UNDESIRABLE EFFECTS AND TOXCITY

As of this writing, there are no reports of side-effects or adverse reactions associated with *P. vulgaris*.

VIII INTERACTION WITH CONVENTIONAL DRUGS

There are no known drug interactions with *P. vulgaris* found in the literature.

IX MODE OF ADMINISTRATION

P. vulgaris can be used fresh, or dried for later use, it is made into a tincture, as infusion, or an ointment for topical use. Internally, selfheal has been used in Western medicine for treating hemorrhage and to decrease excessive menstruation, externally in Western medicine, it is used for minor injuries, sores, burns, bruises, sore throat, mouth inflammations, and hemorrhoids (whole plant). The juice of a crushed stem will sooth nettle stings, minor bouts with poison ivy, insect bites and stings.

X DOSAGE

To use as an infusion, take 1 oz. of *P. vulgaris* in 1 pint of boiling water. Let it cool slightly. Drink 1 wineglassful several times a day. To use an extract, soak 1 teaspoon of this plant in 1 pint of brandy or whiskey for a few days. Or to calculate in weigh, for either adult or children, 9-15 g of *P. vulgaris* taken is most suitable per day.

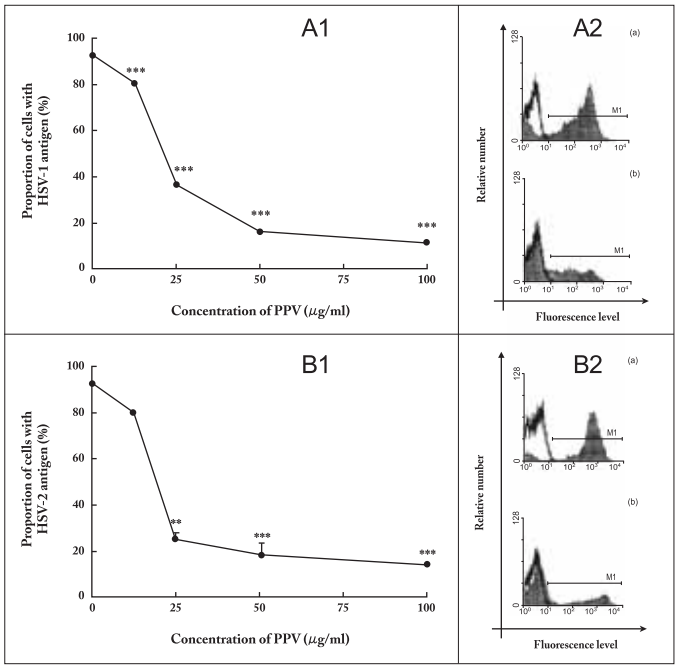

Figure 5. Effect of polysaccharide extract of prunella on antigen expression of HSV-1 (A) and HSV-2 (B) in Vero cells. Both HSV-positive cells descreased dose-dependently with increasing concentration of the polysaccharide (A1 and B1). Cell cycle analysis by means of immunostainings and flow cytometry revealed that the infected cells in M1 stage were significantly reduced in the presence of the polysaccharide (A2b & B2b) in comparison to the controls (A2a & B2a), suggesting that this polysaccharide downregulated the HSV antigen expression[3].

XI DURATION OF APPLICATION

Owing to the different recommendations of the manufacturers, topical preparations should not be used without any prior consultation with professionals.

XII REGULATORY STATUS

Canada: *P. vulgaris* is included in Class 4 and is classified as "Secondary Noxious Weed Seeds" in the Weed Seeds Order, 2005.

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Welcome Message from the Chairman Hong Kong Pharmacy Conference 2005

Kwong, Benjamin YS

Dear friends & colleagues,

The philosophy of Balance is rooted in all Chinese since the invention of Yin Yang. We all believe that Striking the Right Balance of it can lead us to a natural, healthy, happy and fruitful life. We all understand that any unset of this balance can bring us an unnatural, unhealthy, unhappy and dismantling life. Every one of us is trying our best to strive for the balance, the optimum balance.

This year Pharmacy Conference 2005, once again has got the six organizations including the Chinese University of Hong Kong, the Hospital Authority, the Department of Health, the Practicing Pharmacists Association of Hong Kong, the Society of Hospital Pharmacists of Hong Kong and the Pharmaceutical Society of Hong Kong come together to hold the 18th Hong Kong Pharmacy Conference. The organizing committee realizes that the importance of right balance, therefore we have chosen the theme for this year as **Striking the Right Balance: Doing it together.**

Surely as health care professionals, we are much concern on health care issues. This element of balance has been greatly emphasized in the past months. Last year, our conference concentrated on partnership with patients. This year we will put forward a more sensitive issue to you all which is how we can strike the right balance? Mentioning the right balance on health care, we may have to look at it at the Macro, Meso and Micro three different levels to complete the picture. In any society including Hong Kong we need a macro balance on how fiscal budget and health policy fit into the health care financing. At meso balance, we need to decide the differentiated role of each health care provider. At micro level, we pharmacists ourselves have to strike our own balance to fit in to the macro and meso levels.

To enlighten our fellow colleagues in the pharmacy fields this year, we are honour to able to invite our new Secretary for Health, Welfare & Food, Dr. York Chow to share with us his insight on the new model of health care financing in his keynote speech on Day 1. Do you want to know how health care providers including pharmacists can play a part in it? Towards the end of this year, the Health, Welfare & Food Bureau will release a consultation paper on health care financing. It is the right moment for us to know more about it, to prepare for it and to react proactively to it.

Follow a speech on macro balance; we are delighted to have the President of the Hong Kong Medical Association, Dr. Choi Kin to enlighten us on the partnership role of pharmacists in primary health care. We all aware of the different roles of each of the health care professionals play in the primary care setting. How pharmacists could integrate and partnering in as a member of the primary care team? If you want to know how you could play a role and being recognized by the public, our next prestigious speaker Dr. Janet Engle would tell you so. Dr. Engle is a well-known pharmacist in North America and she has ample of experiences to share with us how pharmacists can play a leading role in her two day speeches.

We cannot complete the picture without the micro balance. Mr. Fred Ayling, the Mastermind of the Continuing Professional Education Program of the Royal Pharmaceutical Society of Great Britain will present to us how pharmacists ourselves look at this new requirement in response to the changing environment in our pharmacy practicing field. He will also share with us how they can start from zero to where they are now. Apart from these main theme speeches, we also have packed concurrent sessions on day 2 with internationally famous and locally well-known speakers. Our topics cover a wide range of interests, from clinical like setting up a Poison Centre to treatment of Schizophrenia, from community like fall prevention to Drug Information hotline, from Chinese medicine like identification of herbs to drug interaction with our daily consumables food and fruit.

Only after knowing what is the right balance first before we can start striking for it. Therefore, I urge you all to come to this year Hong Kong Pharmacy Conference to apprehend what others think about of the right balance. We then as a pharmacist profession will know how to strike for the right balance by doing it together among ourselves, and with other health care providers and with the general public. I am glad to inform you that the registration fee remains unchanged this year. With such a packed program with all these prestigious, renowned scholars as our speakers and a very exhilarating conference dinner, I highly recommend all registered pharmacists, both locally and overseas, to enroll to this year Hong Kong Pharmacy Conference: **Striking the Right Balance- Doing it Together** on 15th & 16th October 2005 at Kowloon Shangri-La Hotel, Hong Kong.

On behalf of the Organising Committee, I would like to thank you ALL for your full support to the Hong Kong Pharmacy Conference. I look forward to seeing you ALL.

Yours truly,

Benjamin Y S Kwong
Chairman, Conference Organising Committee
Hong Kong Pharmacy Conference 2005

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Hong Kong Pharmacy Conference 2005

Conference Theme " Striking the Right Balance - Doing it together"

Day 1 Saturday, 15 October 2005

Time	Programme Venue:	Speaker
1:30 - 2:30 p.m.	Registration	
2:30 - 2:40 p.m.	Opening Ceremony	
2:40 - 2:50 p.m.	Welcome Address by Conference Chairperson	Mr. Benjamin Kwong
2:50 - 3:00 p.m.	Officiating Speech: Title: Healthcare and Pharmacist	Dr. York Chow
3:00 - 3:50 p.m.	Theme Speech 1: Leadership in Pharmacy - Who, How, Where To?	Dr. Janet Engle
3:50 - 4:20 p.m.	Tea Break, Exhibition & Poster Display	
4:20 - 5:05 p.m.	Theme Speech 2: Pharmacist & Clinician Collaboration - HKMA Diabetes Care	Dr. Choi Kin
5:05 - 5:50 p.m.	Theme Speech 3: Pharmacy Continuing Education in UK - a long and winding road	Mr. Fred Ayling
5:50 - 7:00 p.m.	Cocktail, Exhibition & Poster Display	
7:00 - 10:00 p.m.	Conference Dinner	

Day 2 Sunday, 16 October 2005

	" Striking the Right Balance - Doing it together"		
8:00 - 9:00 a.m.	Registration & Breakfast		
	Early Clinical Case Presentation		
8:00 - 8:30 p.m.	Pharmaceutical Care Plan for Outpatient Disease Management in Hypertension (UIC speakers)	Pharmaceutical Care Plan for Outpatient Disease Management in Diabetes (UIC speakers)	Use and Interpretation of Liver Function Tests (UIC speakers)
8:30-9:10 p.m.	Pharmacist Continuing Education - The Way Forward: Working group under the Pharmacy & Poison Board		
	Concurrent Session I - Beyond Your Mind	**Concurrent Session II - Beyond Western Medicine**	**Concurrent Session III - Community Care - Beyond Dispensing**
9:10 - 9:20 a.m.	Welcome and Introduction	Welcome and Introduction	Welcome and Introduction
9:20 - 10:10 a.m.	IA Setting up a Poison Center: An experience sharing from the US Dr. Heather Ulrich	IIA TCM & Western Medicine - the infernal affair Mr. Kim Ng	IIIA Role of Community Pharmacist *Dr. Janet Engle*
10:10 - 11:00 a.m.	IB The skills of Pain Management - Experience sharing from the US *Speaker from UIC*	IIB "How to identify the confused Chinese Materia Medica in Hong Kong market" *Dr Zhao Zhong Zeng*	IIIB Fall Prevention: Are we meeting the Challenge? *Dr. Bernard Kong* Fall Prevention: How could community pharmacist play a role? Mr. So Yiu Wah
11:00 - 11:30 a.m.	Morning Tea Break, Exhibition and Poster Display		
11:30 - 12:20 p.m.	IC "Stigmatizing experience and structural discrimination associated with the treatment of schizophrenia in Hong Kong" *Dr. Lee Sing*	IIC Herb-Drug interactions: the Good, the Bad, and the Indifferent *Prof. Thomas Chan*	IIIC Community Pharmacist Hotline - Are you a walking encyclopedia? If not, what can you do if a patient asks things that you have no idea at all? *Mr. Michael Yim*
12:20 - 1:45 p.m.	Lunch		
1:45 - 3:30p.m.	Special Interactive Panel on Self-financed Items (SFIs) Panel Members: Representatives from HK General Chamber of Pharmacy Ltd., Chain Pharmacies, HKAPI, Patient group and the Hospital Authority		
3:30 - 3:50 p.m.	" Striking the Right Balance - Doing it together"		
3:50 - 4:00 p.m.	Closing Remarks		

The Practising Pharamcists Association of Hong Kong President Report 2004

Chung, Billy

Looking back...

It's the best time for us to take a pause and look back to review what we have achieved in together with you for the past year. Internally, we have been extremely busy in managing the Association's affairs in a most transparent manner, following the established GC guidelines since 2003 and at the same time, working closely externally, through networking, with you and various professional, academic, industrial and institutional partners.

There were numerous functions which my colleagues have successfully organised wholly for your benefits for the last year, would it be for your welfare, social enrichment, continue education, communication skill improvement, job prospective or for the future development of our profession in the community, there is only one very important thing my colleagues and myself are affirmative of, without your active participations and contributions, all meaningful events would have become quite meaningless to the Association.

Your profound interest will always be our top priority!

Looking ahead...

There are numerous ongoing events that could consolidate our specialised functional role in the community as the primary care provider. Just name a few, the Wong Tai Sin Social Welfare Education Program in training the drug knowledge for the social workers, nurses, home carers, volunteers and the elderly; the Centre for Health Protection Surveillance System Department of Health in monitoring the possible outbreak of infectious diseases in the community; the 4P Drug Compliance and Counselling Services (DCCS) for the referred patients from the HA with chronic diseases and the Neighbourhood Pharmaceutical Care Scheme (HKW Cluster) in working with family physicians to outreach for the elderly residing in nursing homes.

The implementation of the HA Central Drug Formulary in mid July 2005 by sending SFI prescriptions to the private sector may create not only business opportunity for the community but under our lawful dispensing control, this may also serve as the very first glimpse of hopeful light to the path of SDP in the community. Through our persistent effort and teamwork, we could achieve our ultimate goal and meet the immense challenges in creating a new community order in the practice of pharmacy.

I remain, on behalf of my new elected colleagues for the 34th term (2005 - 2006), at your service, as always! Let's work hard together in unity and make our dream come true.

Name	*Title*
Mr. Billy Chung Wing Ming	President
Ms. Dorothy Chin Kin Main	Vice-President
Ms. Iris Jacqueline Chang	Vice-President
Ms. Catherine Yeung Pui Wa	Hon. Secretary
Mr. Wong Or	Hon. Treasurer
Mr. Chan Yat Ming	G.C. member
Ms. Yvonne Fung Sau Fung	G.C. member
Ms. Irene Kwok Hing Fun	G.C. member

Name	*Title*
Mr. Joe Kwok Chung Man	G.C. member
Ms. Anna Leung	G.C. member
Mr. Lin Kim Fung	G.C. member
Mr. Tang Ting Kwan	G.C. member
Ms. Estella Wang Wai Min	G.C. member
Mr. Jack Wong Lung	G.C. member
Mr. Yip Song Ngai	G.C. member

Prepared by Billy Chung
May 23rd 2005

香港醫院藥劑師學會2005年會長報告

吳劍華

過去一年，社會上發生了很多變遷，在醫療衛生界別裡，猶為複雜，相繼有醫管局高層及衛生福利局局長的請辭，這些事情都在社會上帶來不少沖擊。 新任衛生福利局局長的醫療政策與方向，相應地會左右了藥劑行業的前途和發展。藥劑界因這些轉變，牽動了業內不少矛盾的情緒，帶來了新的挑戰與機遇，同時也感到它帶來強烈的壓力。藥劑行業正站在一個危險的十字路口，我們若不能把握契機，便會失之千里。

2004-05 年工作概況

面對種種轉變，學會的工作已不能單靠我們工餘時間可以應付，我們實在已感到力不從心。醫管局「中央藥物名冊」即將實施，社會各階層也加速了對藥物教育的關注，因此學會的工作焦點，也須作出急速的回應，大量工作已集中在公共藥物教育事務上。「藥物教育資源中心」的工作，更顯得重要，工作量在過去一年已倍增，在此我衷心感謝「資源中心」各位成員努力不懈的幹勁，亦感謝一群熱心的藥劑師，辛勤的參與藥物教育講座的義務工作 (見附件 DERC Program 2004-05)。 今年我們獲得香港聖公會福利協會長者綜合服務中心，頒發傑出義工團體獎，這進一步証明我們所做的工作，已為社會各界認同與接受。

為配合社會對藥劑服務的訴求，我們更史無前例的與香港醫學會聯繫，應邀參與對「醫管局中央藥物名冊」意見的工作小組，又參與他們舉辦的市民教育如「糖尿病木人巷」等項目。我們又積極與其他醫藥專業組織交流，加強藥物教育服務的滲透能力，例如與執業藥劑師協會、醫管局合作，推行「社區藥物輔導」計劃，使市民習慣使用社區資源。

為了建立藥劑師在社會的形象，與醫療專業組織建立溝通渠道是十分重要的，目前與我們建立了互動合作關係的團體，除了香港醫學會外，也包括了「全民健康動力」、吸煙與健康委員會、醫管局、衛生署、衛生防護中心、浸信會中醫藥大學、各醫院及社團等服務中心、病人組織、立法局衛生專業代表的議員等。我們透過支持及參與他們舉辦的公共教育工作，藥劑師在社會上的專業形象，已普

適提高。同時我們也組織了中文大學藥劑系的學生，參與公共教育工作，使我們的新血有直接參與社會服務的經驗，提高他們的組織能力，增加他們對藥劑行業的歸屬感。

近年來由於中醫藥受到不少市民的歡迎，安全使用中藥亦備受關注，我們成功地與浸信會中醫藥大學結為「專業夥伴」，在今年初與浸信會中醫藥大學及中央圖書館合辦「安全使用中西藥物」的教育講座，亦是極受歡迎的項目。我們努力出版藥物教育書刊、宣傳單張等，在明報、蘋果日報、太陽報、「醫藥人」，各報章雜誌等藥物資訊專欄中，已經常看到「藥物教育資源中心」的文章。去年底「藥物教育資源中心」與「醫藥人」出版了「藥」這本書，雖然這本書仍有改善之處，但亦受到普羅市民所歡迎，第一版已售罄。

2005-06年展望

持續推動藥劑教育事務，將會是本會的基本工作方針，我們會繼續與夥伴合作，使市民從不同途徑中得到藥物知識，從而懂得照顧自己的健康。我們已著手建立藥物教育網頁，網頁將會在今年七月中為市民大眾服務，亦希望在年底前與浸信會中醫藥大學出版「安全使用中西藥」的書刊，使市民能直接得到用藥知識。對會員方面的服務，我們會繼續改善現時的網頁，加速實現「臨床藥劑」資料庫及資訊平台，相信在今年夏季，會員便可在網上交流專業知識。由於當前的工作量大而且迫切，容許我在此呼籲，希望新的、舊的、老、中、青的藥劑師們，齊來參與，攜手共建。

制訂標準藥物名冊有助醫療融資

鄺耀深

近幾年香港的醫療服務都有很多改革。香港與其他發達國家一樣面對同樣的問題，就是醫療開支已是政府的一個沉重承擔。隨着人口老化，醫療科技日新月異，醫療的需求及要求又高又大，加上現今生活方式及生活環境都較以往容易引發疾病，都市人很容易忽略了健康的重要。有病才打算的心態非常普遍，預防勝於治療的想法似乎大家都忘記了。看見時下的小孩過於肥胖，醉酒駕駛引起車禍非常普遍，吸煙引起的身體禍害等等，其實都對現時的公共醫療做成沉重的負擔。

最近醫管局推出了一套名為標準藥物名冊給公眾諮詢，這名冊列出日後醫管局只提供一系列的藥物，在此名冊以外的藥物病人就需要自己購買。有一些專科用的藥物將會有用藥指引，不符合指引內使用，醫生便會叫病人自行購買。

原則上香港藥學會贊成有此標準藥物名冊。近十年間，市場有很多新藥推出，藥廠在治療領域中常常有突破性的發現，好像在愛滋病、癌病等。不過，亦因為推出太快，往往有些未能經得起時間的考驗便要停止使用。有一些藥物可能要付出高昂的價錢而換取極小的好處，是否值得那就見人見智。不過若果有些療效顯著又安全的好藥，但只可以有錢的人才可得到治療的話，那未免講不過去。以前說心臟病是有錢人病，現在患者不分老嫩貧富都可得到治療，這才是一個公義的社會。

這個名冊對日後解決醫療融資的問題會有一定的幫助。在推行的時候，一定要有適當的配套，例如要病人自購藥物應去那裏購買，日後會不會有一個公眾委員會去釐定那些藥物該列入名冊內，那些不應該等。若沒有這些配套，日後執行時可能會發生很多不必要的爭拗。

藥物名冊的理念是對的。不過我們必須要小心，在制訂名冊、監察執行的過程必須公平公開及公正。我們要嚴肅處理這問題。香港藥學會希望香港人仍然可以享受到最有成本效益的醫療服務及藥物，更希望大眾能共同承擔，讓所有香港人以最合理的價錢得到最佳的服務質素。

二零零五年三月五日

鄺耀深
香港藥學會會長

Note: In response to the new Hospital Authority (HA) policy on drug, standard Drug Formulary (SDF), the three pharmacists societies have put forward this communication to the HA.

Response to Public Consultation on the Standard Drug Formulary

Ng, Kim Wah

29th April, 2005

Room 216,
Hospital Authority Building,
147B Argyle Street,
Kowloon

Dear Sir / Madam,

The Hospital Authority ("HA") is now soliciting the public's comments on its proposal to establish a Standard Drug Formulary ("HASDF"). This correspondence is collectively authored by the General Committee of the Society of Hospital Pharmacists of Hong Kong ("SHPHK") as the Society's official response.

SHPHK has throughout its history staunchly supported its members and the health community at large in promoting the rational use of drugs. In this regard, SHPHK supports HA's initiative to set up the HASDF based on HA's stated objectives to provide equitable access to, and to promote rational use of, cost-effective drugs of proven safety and efficacy.

SHPHK further believes that *these should be the sole objectives*. For this reason, it will be inappropriate to include any financing elements beyond cost-effectiveness in the design of a Standard Drug Formulary. To this extent, SHPHK urges HA to carefully review and revise two areas in its HASDF proposal:

First, HA's proposal describes a category of "special drugs" which are to be prescribed as formulary items only when certain clinical criteria are met, or else they have to be prescribed as patient self-financed items. In practice, this creates a cause-and-effect relationship between the clinical judgement of a clinician and financial implications for his patient. SHPHK is concerned that this will tempt a patient who intends to acquire medication under the "special drugs" category to seek to interfere with the doctor's clinical judgement to the patient's favour through some indiscreet means. SHPHK urges HA to carefully evaluate the impact, and possible pressure, this will bring upon clinicians while interacting with patients.

Second, SHPHK contends that there should not be a class of "non-formulary drugs with safety net". Drugs proven to be of significant benefits should simply be included as "standard" or "special" items in the HASDF, whereas any others drugs should be non-formulary and financed by patients themselves. To have an intermediate class of drugs between the two, such as the presently proposed "non-formulary drugs with safety net", is to go beyond HA's own stated objectives for the HASDF and to corrupt those objectives with financing considerations.

This is not to say SHPHK is dismissing the need for a safety net altogether. For the sake of equitable access, SHPHK supports the *general notion* that a safety net should be set up for patients who cannot afford their treatment. In fact, such a safety net already exists - in the form of the medical fee waiver mechanism. As long as this mechanism is sufficient for ensuring equitable access to medical treatment, SHPHK believes there is no use for, and it is inappropriate to have, an extra safety net dedicated to financing specific drugs.

While it is SHPHK's view that it is beyond the scope of a formulary policy to tackle financing issues, SHPHK recognises that financing the class of drugs the current HASDF proposal lists as "non-formulary drugs with safety net" is a very real problem. SHPHK proposes the following as a possible solution:

In its proposal of a targeted subsidy model for "non-formulary drugs with safety net", HA cites the principle: *"Those who can afford should pay"*. SHPHK agrees with this principle and further advocates that *it should be applied across the board to the entire HASDF*. Specifically, SHPHK propose that HA should revise the current drug charging schedule for "general" and "special" drug items with a view to raise the charges to a level that supports the principle cited above. (This assumes that a robust medical fee waiver mechanism exists to ensure equitable access.) The positive balance generated from supplying relatively inexpensive drug items should then be used to cross-subsidise relatively expensive items. SHPHK hopes this financing arrangement will make it practical to abolish the class of "non-formulary drugs with safety net" and allow drugs of that class to be admitted into the HASDF as "general" or "special" items, as they should be.

HA has stated that it is open to suggestions regarding the supply mechanism for non-formulary drugs. SHPHK states its position on this matter as follows:

Given that the class of "non-formulary drugs with safety net" can be abolished, there remain three types of drugs that are non-formulary: (a) drugs with preliminary clinical evidence only; (b) drugs with marginal benefits but at significantly higher cost; (c) life style drugs. SHPHK argues that the supply of such drugs contradicts HA's own principle of rational use of public resources, and hence HA should play no role in it beyond making provisions for HA doctors to prescribe them in accordance with patients' choice. SHPHK proposes that community pharmacies, in their capacity as Authorised Sellers of Poisons bound by legal and professional requirements to supply safe and efficacious drugs to the public, should supply, and is competent in supplying, non-formulary drugs, as long as public resources are not used to compete with the free market. SHPHK further advocates that HA should actively cooperate with community pharmacies for the benefit of patients by coordinating the distribution of information useful to patients, for example, the availability of non-formulary drugs and the locations and operating hours of community pharmacies.

SHPHK has arrived at the positions stated in this correspondence through its own consultation process as follows:

(1) On 23rd February, 2005, an open forum was jointly held by SHPHK, the Practising Pharmacists Association of Hong Kong, and the Pharmaceutical Society of Hong Kong to discuss HA's draft of the HASDF proposal. Pharmacists from different sectors attended and expressed their opinions.
(2) Comments were solicited from SHPHK members through electronic mail.
(3) The General Committee of SHPHK held meetings to discuss the matter, consolidate views, and formulate this correspondence.

SHPHK commends HA on taking a bold, proactive step towards rational use of drugs, and looks forward to working with HA to implement changes brought on by the HASDF that are beneficial to patients, the general public and the society.

Yours Sincerely,

Ng Kim Wah
President
The Society of Hospital Pharmacists of Hong Kong
On behalf of the General Committee

HA Standard Drug Formulary Public Consultation

The Practising Pharmacists Association of Hong Kong

The Hospital Authority
Room 219N 2/F Hospital Authority Building
147 Argyle Street
Kowloon HK

April 29th 2005

Objective:

The objective of this document is to present the stance of the Practising Pharmacist Association of Hong Kong (PPAHK) in response to the public consultation of the draft discussion paper put forward by the Hospital Authority (HA) on 18 February 2005 " Introduction of a Standard Drug Formulary in the Hospital Authority - the Legislative Council Panel on Health Services"

Background:

The PPAHK General Committee Members and association members have scrutinized the proposal, while taking into consideration the short term and long term implications on the effects of the suggested actions on the welfare of the general public, the public health sector (HA), and the private healthcare providers.

It is of our ultimate interests to enhance and protect the interests of the public to receive high quality, affordable, and sustainable healthcare services in the short, medium, and long term.

In order to meet the needs of the public within HA's finite budget situation in a long term and sustainable fashion, Dr York Chow has declared that a policy of focusing the public medical services to the poor, to disasters, and to the generally unaffordable high-tech life saving procedures.

Consultation:

The Presidents of the three professional associations, namely the PPAHK, SHPHK and PSHK, have consulted its members by conducting an open forum on 23 Feb 2005 to collect opinions and recommendations on the draft discussion paper. Pharmacists from different disciplines (community, hospital, industry, academia) were present to express their viewpoints at their respective angles. It was in common stance that our goal was to take a long term view of the recommendations proposed in the draft paper.

An equal balance between the public and the private healthcare system is of pinnacle importance to create the optimal healthcare environment for the public's long term benefit. An equal balance can be defined as a system where the HA focuses its resources to serving hospital in-patients, the poor and disadvantaged, to emergencies and disasters, and to the generally unaffordable catastrophic illnesses, usually requiring extensive hospital services while the private sector provides for the general prevention, cure, and management of illnesses in a primary healthcare setting. It will be in a teamwork fashion where the sharing of healthcare responsibilities between the HA and the private sector which creates a synergy that works for the long term benefit of patients and healthcare providers.

Meetings with the President and Council Members of the Hong Kong Medical Association (HKMA) were held to share views and discuss constructively on other possible alternative options available to the HA. It was obvious that the HA could not provide free medicine for all without a bottom line. HA must clearly define the role they played in the medical service market and prioritise the resources available to better serve the more needy group in our community. The suggested options at the consultations were as follows:

1. Title of the Drug Formulary

It was almost in full agreement that there should be one uniform formulary to be used in all HA hospitals to create a more systematic and fair drug delivery system for HA patients. It is also necessary to establish a list of basic and general use drug items in view of the finite HA budget situation. However, the name of the formulary may be called the "Hospital Authority Drug Formulary" without the word "Standard" so as to avoid misunderstanding in the medical fields.

2. Drug Groups

Drugs not included in the "general use" and "special" categories of the formulary but are necessary for the continuing care of patients under certain clinical conditions, the HA should, therefore, state clearly that drugs outside the HA Drug Formulary or the "Non-Standard Drugs" are of equal clinical importance in clinical applications and are qualified for insurance coverage.

3. Safety Net

It is essential for the HA to define clearly "patients with difficulties" and in how the drug expenses could be reimbursed.

4. Self Financed Drugs Supply

It was generally in full consensus that the supply of Self-Financed Items (SFIs) should be left to the private market unless for the drugs that are not readily available or cannot be effectively supplied in the market. The HA should focus its resources and attention to further improve the quality of health services to in-patients and leave the drug supply of out-patients to the private market.

The pharmacy profession understands that the matter on SFIs and the HA Drug Formulary was not only a strategic decision to control the drug expenditures in the public hospital system but would ultimately become an important corner stone of a healthcare financing model in meeting the demands of drug supply for the general population in Hong Kong. Therefore, it is of paramount importance that we present our views and recommended solutions on the mechanism of drug supply in a strategic and yet pragmatic manner.

It is our vision to provide to the community high quality and long term pharmaceutical care. Community pharmacists can fill the gap that HA is not able to fulfill at the current moment and in the foreseeable future. There have been 4 options proposed by the discussion paper in the supply of the SFI drugs.

Option A : Patients Purchase SFIs in Community Pharmacy

Most members believe this is the best and most effective method to supply the SFI drugs for the following reasons:

a) HA can focus its limited resources to deliver their core objectives namely, focusing on hospital in-patients, serving the poor, disasters, and catastrophic illnesses.

b) Out-patients can make more use of the under-utilized private community pharmacies and create opportunities to develop a more balanced healthcare system.

c) Patient-pharmacist relationship develops easily and quickly in a community pharmacy setting and patients can confide in their pharmacist to obtain free and long term health and pharmaceutical care services. When community pharmacists are readily available, effective pharmaceutical care and continuous follow-ups are possible. This is the key to a long term therapeutic success. At present, the HA is only able to provide for a one-off dispensing activity and virtually no effective patient follow-up mechanism. If this form of non-optimal pharmaceutical care and services is allowed to continue, it will only lead to ineffective drug therapy caused by patient's incorrect drug administration, drug non-compliance, polypharmacy, drug-drug and food-drug interactions. One typical example is that some HA hospitals patients fail to have their blood glucose level controlled after receiving oral insulin-inducing anti-diabetic drugs despite their full compliance with drug treatment. Upon free counseling at the local community pharmacy, it was found that the patients have waited too long to eat their meals after taking the medications therefore wasting the expected effects of the drugs. HA patients have no channel to express their concerns and obtain the necessary advice on what to do in order to reach their therapeutic goal until their next HA appointment 3 months later. In the meantime, the wastage of the money for purchasing the drugs, the patients time and money for the HA visit, and the efforts of the medical staff and the patient is unnecessarily amounted. The role of the local community pharmacist is crucial to fill this service gap in order to provide effective pharmaceutical care at the present time and in the future. Even though the patient initially needs to take their prescription to their community pharmacy to fill and may feel slightly inconvenienced, it is to their ultimate benefit to establish a good relationship with a pharmacist that can provide long term and free advice on SFIs as well as HA formulary drug items.

Our Recommended Solutions:

i. Patient Convenience

- A total number of 446 retail pharmacies in the whole of Hong Kong spreading across 18 districts with an average of 20-30 community pharmacies to each district, allows patients to choose a pharmacy that is convenient for them, whether it is in the vicinity of their place of work or residence, to obtain their supply of SFIs.
- The Public Private Partnership Programme (4P) on Drug Compliance and Counseling Service (DCCS) launched last year can be used as the foundation to build the SFI programme
- Community pharmacists have a better opportunity to provide a higher level of long term pharmaceutical care as compare to HA hospital pharmacists. This will lead to a higher level of therapeutic success while eliminating wastage of time and money.

ii. Variable Pricing

- Pricing variations among competing stores will not be entirely out of proportion as the market will generally self-regulate itself. Minimal differences in price will create healthy competition and usually works to the benefit of consumers in the long term.
- Consumers can have a freedom of choice to patronize a pharmacy that offers the best value for their money.

iii. Parallel Import/ Fake Drugs

- The Hong Kong Department of Health has a strong regulatory system; and the Customs and Excise Department has already established an effective consumer hot-line to fight against fake drugs.
- The PPAHK is considering the establishment of a central servicing unit to ensure the quality of drugs purchased for the convenience of community pharmacists.
- The Hong Kong General Chamber of Pharmacy have been a pioneer member of the "No Fakes" Pledge Scheme, established by the Intellectual Property
  Department pledging to sell authentic products only. The members of the Hong Kong General Chamber of Pharmacy will have to comply with this Pledge Scheme and any public complaints can be made through the Chamber's hot-line to fight against fake drugs.

Option B: Inviting Community Pharmacies to Operate in HA Hospitals

Our views on this option are basically the same as in option A. The point to mention is that it may be inconvenient for the patients to travel back to the hospital to obtain any form of advice or pharmaceutical care after filling the prescription.

To bid for the tender by big conglomerates, which have financial might and a wealth of experience in running community pharmacy, against those small independent pharmacies creates unfair competition.

Option C: HA Sells SFIs

It is inadvisable for HA to supply SFIs in this manner for the following reasons:

a) HA dilutes its efforts and limited resources to deliver services over and beyond their core functions.

b) HA directly competes with the private market for primary care services and SFI supply with its intrinsic business advantages as a government organization namely, low purchasing price and bulk purchase abilities. Private healthcare providers, with no affiliation with government agencies, will undoubtedly quickly wither when operating in such unfair business environments. Eventually, all patients will depend on the HA causing the HA bubble to burst in an accelerated manner.

c) Patients will continue to just receive the one-off dispensing services offered by the HA as at present and they are also denied the freedom of choice to enjoy effective pharmaceutical care and free counseling from community pharmacists.

Option D: Other Alternatives or Any Combinations of the above

Since the Option A is the preferred choice, community pharmacists are ready and committed to play our functional role more effectively as the "gatekeeper" in the primary healthcare services in educating the public on the safe use of medications, managing the chronic diseases and improving the public healthy lifestyle. Working closely together with the frontline healthcare professionals in the field, such as family physicians, community nurses, social workers and home carers, one could definitely contribute synergistically to lower the HA expenditure on primary care and the HA can concentrate mainly on the secondary and tertiary care services for the patients.

Conclusion:

The PPAHK supports the HA in the introduction of the HA Drug Formulary and welcomes the opportunity to supply the SFIs by the private community pharmacies. This professional partnership will become the first step to developing a more balanced and sustainable healthcare system. We believe that continually higher levels of pharmacy practice would evolve as the SFIs prescriptions will create significant market forces to drive quality service, lower prices, and prevention of fake drugs. Thereby, the general population of Hong Kong will benefit from such comprehensive and effective services.

The Practising Pharmacists Association of Hong Kong
4/F Duke of Windsor Social Service Building
15 Hennessy Road
Wanchai
Hong Kong

Active ingredient:
A combination of Ezetimibe and Simvastatin

Presentation:
Available in a pack of 30's with the following strength combination
10 mg Ezetimibe / 10 mg Simvastatin
10 mg Ezetimibe / 20 mg Simvastatin
10 mg Ezetimibe / 40 mg Simvastatin
10 mg Ezetimibe / 80 mg Simvastatin

Pharmacological Properties:
Simvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes an early and rate-limiting step in the biosynthesis of cholesterol. Ezetimibe selectively inhibits the intestinal absorption of cholesterol and related plant sterols.

Indications:
VYTORIN is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, Triglycerides and non-high-density lipoprotein cholesterol, and to increase high-density lipoprotein cholesterol in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia.

VYTORIN is indicated for the reduction of elevated total cholesterol and LDL-C levels in patients with Homozygous Familial Hypercholesterolemia, as an adjunct to other lipid-lowering treatments or if such treatments are unavailable.

Dosages and Administration:
The recommended usual starting dose is 10 / 20 mg per day. Initiation of therapy with 10 / 10 mg per day may be considered for patients requiring less aggressive LDL-C reductions. Patients who require a larger reduction in LDL-C (greater than 55%) may be started at 10 / 40 mg per day. After initiation or titration of VYTORIN, lipid levels may be analyzed after 2 or more weeks and dosage adjusted, if needed.

Contraindications:
Hypersensitivity to the active substances or to any of the excipients; active liver disease or unexplained persistent elevations of serum transaminases; pregnancy and nursing.

Precautions:
Myopathy / Rhabdomyolysis - Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

Side effects:
VYTORIN has been evaluated for safety in more than 3800 patients in clinical trials. VYTORIN was generally well tolerated. The following common drug-related adverse experiences were reported (≥ 1/100, < 1/10):
Gastrointestinal disorders - flatulence
Musculoskeletal and connective tissue disorders - myalgia
Nervous system disorders - headache

Drug Interactions:
Interactions with lipid-lowering drugs that can cause myopathy when given alone. The risk of myopathy is also increased by the following lipid lowering drugs, (Gemfibrozil, other fibrates and Niacin when taken more than 1g per day), that are not potent inhibitors of CYP3A4, but which can cause myopathy when given alone.

The risk of myopathy / rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol, particularly with higher doses of VYTORIN.

Forensic classifications:
P1S1S3

Great News ....

Continuing Education Units (CEUs) for Authors of Articles in the HKPJ. At the most recent meeting of the Pharmacy Central Continuing-education Committee (PCCC), it was decided that CEU would be awarded to authors of articles published in the HKPJ. For each issue, the Editorial Committee, led by the Managing Editor, will choose an article from all the published articles in that issue, for PCCC to use for CE purposes. The author(s) is(are) responsible for setting questions for the approved CE article. Primary authors are entitled to receive 6 CEUs and other co-authors of the same CE article are entitled for 4 CEUs granted by PCCC. For details on how to get CEU, please refer to the article named "PCCC Continuing Education Units (CEU) Accrediting System" [HKPJ 2002;11(2):79-80].

Great news to boost the professional standard and recognition of the contributions to the HKPJ!

Seeking The Best Chance for a Cure in Chronic Hepatitis

PEGASYS®
peginterferon alfa-2a (40KD)

Breaking News
PEGASYS® **HBV** Indication
Now Approved !

The ONLY
Pegylated Interferon Supplied as a Pre-filled Syringe !

Prescriber-friendly & Patient-friendly

Simple fixed dose, ready-to-inject solution

Unsurpassed Efficacy in Both

– Chronic Hepatitis B

- Statistically significant and superior benefit versus lamivudine.[1,2]

– Chronic Hepatitis C

- Consistent high overall response rates in large, randomized multicentre clinical studies.[3]

Full prescribing information is available upon request

Reference:
1. Marcellin P et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2004;351:1206-17.
2. Lau G et al. 55th Annual Meeting of American Association for the Study of Liver Diseases.
3. Hadziyannis SJ et al, Peginterferon alfa-2a and ribavirin combination therapy in chronic hepatitis C, Ann Intern Med. 2004; 140:346-355.

Roche

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