# HONG KONG PHARMACEUTICAL JOURNAL

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*The Practising Pharmacists Association of Hong Kong*
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# The same great benefits.

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## Proven to reduce CV events by up to 50% in multiple major CV outcomes trials.[1-9]

- Proven CV outcomes evidence from landmark trials[1-9]
- Efficacious LDL-C lowering[10,11]
- Well established renal safety profile in CKD patients[12,13]
- NO dosage adjustment in patients* with renal impairment[10,14]

*excluding kidney transplant patients

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Power to do more


**References 1.** Schwartz GC, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes - the MIRACL Study: A randomized controlled trial. JAMA 2001;285(13):1711-1718 **2.** Amarenco P, et al. High-Dose Atorvastatin after Stroke of Transient Ischemic Attack. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study (SPARCL). N Engl J Med 2006;355(6):549-59 **3.** LaRosa JC, et al. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. N Engl J Med. 2005;352:1425-35. **4.** Sever PS, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003;361:1149–58 **5.** Colhoun HM, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–96 **6.** Pasceri V, et al. Randomized Trial of Atorvastatin for Reduction of Myocardial Damage During Coronary Intervention. Circulation. 2004;110:674-678 **7.** Cannon CP, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495-504 **8.** Pedersen TR et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 2005;294(19):2437-45 **9.** Athyros V et al. Treatment with Atorvastatin to the National Cholesterol Education Program Goal Versus "Usual" Care in Secondary Coronary Heart Disease Prevention. The GREek Atorvastatin and Coronary-heart-disease evaluation (GREACE) Study. Curr Med Res Opin 2002;18:220-8. **10.** Lipitor® (atorvastatin) Prescribing Information. Pfizer Corporation Hong Kong Limited. Version September 2011. **11.** Law MR et al. BMJ 2003;326:1423-1427 **12.** Shepherd J et al. Effect of Intensive Lipid Lowering with Atorvastatin on Renal Function in Patients with Coronary Heart Disease: The Treating to New Targets (TNT) Study. Clin J Am Soc Nephrol 2007; 2: 1131-1139 **13.** Colhoun HM et al. Effects of Atorvastatin on Kidney Outcomes and Cardiovascular Disease in Patients With Diabetes: An Analysis From the Collaborative Atorvastatin Diabetes Study (CARDS). Am J Kidney Dis 54:810-819 **14.** KDOQI Clinical Practice Guideline For Diabetes and CKD: 2012 Update. Am J Kidney Dis 2012;60(5):850-886.


**LIPITOR ABBREVIATED PACKAGE INSERT 1. TRADE NAME:** Lipitor® **2. PRESENTATION:** The tablets for oral administration contain atorvastatin calcium equivalent to 10, 20, 40 or 80 mg atorvastatin **3. INDICATIONS:** Adjunct to diet for the treatment of patients with elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides and to increase HDL-cholesterol in patients with primary hypercholesterolemia (heterozygous familial and non-familial hypercholesterolemia), combined (mixed) hyperlipidemia (Fredrickson Types IIa and IIb), elevated serum triglyceride levels (Fredrickson Type IV), and for patients with dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet. For the reduction of total cholesterol and LDL-cholesterol in patients with homozygous familial hypercholesterolemia when response to diet and other non-pharmacological measures are inadequate. Reduce the risk of myocardial infarction, stroke, revascularization procedures and angina in adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease. Reduce the risk of myocardial infarction and stroke in patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension. Reduce the risk of non-fatal myocardial infarction, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF and angina in patients with clinically evident coronary heart disease. Atorvastatin is also indicated as an adjunct to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: a. LDL-C remains ≥ 190 mg/dL or b. LDL-C remains ≥ 160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other CVD risk factors are present in the pediatric patient. **4. DOSAGE:** The recommended starting dose of Lipitor is 10 or 20mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40mg once daily. The dosage range is 10 to 80 mg once daily. After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 2 to 4 weeks, and dosage adjusted accordingly. **5. CONTRAINDICATIONS:** Hypersensitivity to any component of this medication, active liver disease or unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal. Pregnant, breast-feeding, or of childbearing potential who are not using adequate contraceptive measures. Atorvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards to the fetus. **6. WARNINGS & PRECAUTIONS:** As with other lipid-lowering agents of the same class, moderate (>3 x upper limit of normal [ULN]) elevations of serum transaminases have been reported following therapy with atorvastatin. Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggesting liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality (ies) resolve(s). Should an increase in ALT or AST of greater than three times the upper limit of normal persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin can cause an elevation in transaminases. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Myalgia has been reported in atorvastatin-treated patients. **7. INTERACTIONS:** Cyclosporine, fibric acid derivatives, lipid-modifying doses of niacin or cytochrome P450 3A4 inhibitors (e.g. erythromycin, and azole antifungals), clarithromycin, protease inhibitors, diltiazem hydrochloride, itraconazole, grapefruit juice, inducers of cytochrome P450 3A4 (e.g. efavirenz, rifampin), antacids, colestipol, digoxin, oral contraceptives, fusidic acid **8. PREGNANCY AND LACTATION:** Atorvastatin is contraindicated in pregnancy and while breast-feeding. **9. SIDE EFFECTS:** Nasopharyngitis, hyperglycemia, pharyngolaryngeal pain, epistaxis, nausea, diarrhea, dyspepsia, flatulence, arthralgia, pain in extremity, musculoskeletal pain, muscle spasms,myalgia, joint swelling, liver function test abnormal, blood creatine phosphokinase increased

Reference: HK PI (SEP2011) Date of preparation: FEB2013 Identifier number: LIPI0213

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## INSTRUCTIONS FOR AUTHORS

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

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

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

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

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

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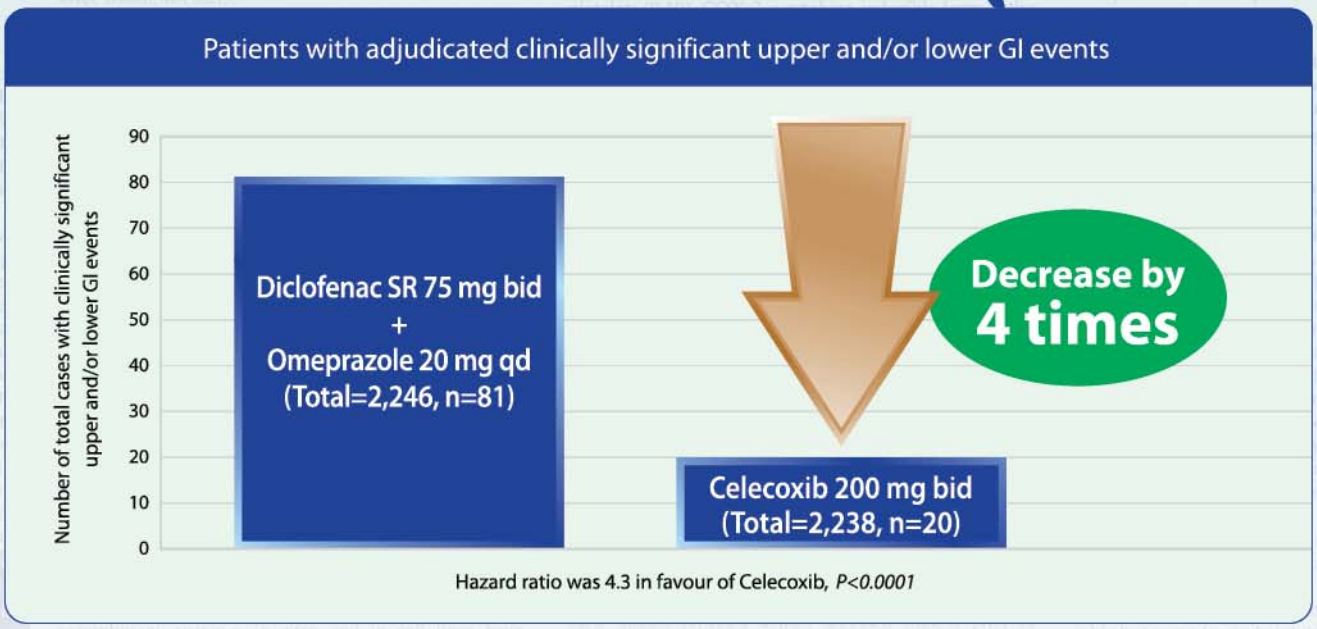
For detail instructions for authors, please refer to the first issue of each volume of HKPJ.

# CONDOR

**C**elecoxib versus **O**meprazole a**N**d **D**iclofenac
in patients with **O**steoarthritis and **R**heumatoid arthritis

## Celecoxib vs. Diclofenac + Omeprazole:

Patients treated with Celecoxib had a **LOWER RISK** of Clinically Significant Upper and/or Lower GI Events[1]




- Proven efficacy in various pain models[2-5]
- The only FDA-approved COX-2 inhibitor[6]
- Option for millions of patients for over 10 straight years[7]


Strengthening confidence across Asia FOR OVER 10 YEARS

CELEBREX®
(CELECOXIB)

**Reference:** 1. Chan FKL, Lanas A, Scheiman J, Berger MF, Nguyen H, Goldstein JL. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR) a randomized trial. J Rheumatol. 2010;37:167-174. 2. Graham DY, Chan FK. Gastroenterology 2008;134:1240-1257. 3. Nadarajah A, et al. Singapore Md J 2006; 47:534. 4. Petri M, et al. J Rheumatol 2004;31:1614-20. 5. Cheung R, et al. Clin Ther 2007;29 [Theme Issue]:2498-2510. 6. Food and Drugs Administration (FDA). http://www.fda.gov. Accessed February 10, 2011. 7. About Celebrex 2010. Available at URL http://www.celebrex.com/about-celebrex.aspx. Accessed Feb 10, 2011.

**CELEBREX ABBREVIATED PACKAGE INSERT** **1. TRADE NAME:** Celebrex **2. PRESENTATION:** Capsules contain either 100mg, 200mg or 400mg of celecoxib. **INDICATIONS:** Adult: For relief of the signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS); management of acute pain (AP) in adults; treatment of primary dysmenorrhea (PD); treatment of the signs and symptoms of low back pain (LBP). **3. DOSAGE:** OA: 200mg OD or 100mg BID; RA: 100 or 200mg BID; AS: 200mg OD or 100mg BID, 400mg OD if no response after 6 weeks; AP & PD: 400mg OD initially, an additional 200 mg if needed on the first day, subsequent days 200mg BID as needed; LBD: 100mg BID. **4. CONTRAINDICATIONS:** Hypersensitivity to celecoxib, aspirin, or other NSAIDs or demonstrated allergic-type reaction to sulfonamide or experienced asthma, urticaria, or allergy-type reaction after taking aspirin or other NSAIDs. Use as treatment for peri-operative pain in the setting of CABG surgery. **5. WARNINGS & PRECAUTIONS:** Increased risk of serious adverse cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal; Patients with known CV disease or risk factors for CV disease may be at greater risk; Caution in patients with hypertensions, fluid retention or heart failure; Can cause serious gastrointestinal events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. Extreme caution in patients with prior history of ulcer disease or gastrointestinal bleeding; special care should be taken as most spontaneous reports of fatal GI events are in elderly and debilitated patients; A patients with symptoms and/or sign suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, Celebrex should be discontinued; Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion; Not recommended in these patients with advanced renal disease; Anaphylactoid reactions have occurred in patients without known prior exposure to Celebrex; Should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin other NSAIDs; Can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events can occur without warning and in patients without prior known sulfa allergy. Patients should be informed about the signs and symptoms of serious skin manifestations and use of drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity; Cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency; Should not be administered to patients with aspirin-sensitive asthma and should be used with caution in patients with preexisting asthma; The pharmacological activity in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions; The concomitant use with any dose of a non-aspirin NSAID should be avoided due to the potential for increased risk of adverse reactions. **6. INTERACTIONS:** ACE inhibitors and angiotensin II antagonists, antacid, aspirin, dextromethorphan, fluconazole, fluvastatin, furosemide, lithium, NSAIDs, paroxetine, warfarin and drugs that inhibit cytochrome P450 2C9. Potential interaction with drugs that metabolized by P450 2D6. **7. PREGNANCY AND LACTATION:** Pregnancy Category C; Pregnancy category D from 30 weeks of gestation onward; Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus; No studies have been conducted to evaluate the effect of celecoxib on the closure of the ductus arteriosus in humans, therefore should be avoided during the third trimester of pregnancy. **8. SIDE EFFECTS:** Abdominal pain; Diarrhea, Dyspepsia; Flatulence; Nausea; Back pain; Peripheral edema; Accidental injury; Dizziness; Headache; Insomnia; Pharyngitis; Rhinitis; Sinusitis; Upper respiratory infection; Rash **Reference:** HK PI (Mar 2011) **Date of preparation:** JUN2011 **Identifier number:** CELE0611 **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

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# Scientific Approach to the Vigilance and Risk Management of Medicines

From the front cover and the thickness of this issue of the HKPJ, readers wouldn't have difficulty to find that this is a special issue devoted to the scientific meeting of the 8th Asian Conference on Pharmacoepidemiology, which will be held in Hong Kong from October 25-27.[1] The goal of this meeting is to address, discuss or exchange ideas relevant to the vigilance and risk management of medicines. Around two hundred researchers and experts from the field of apply pharmacoepidemiology in different countries will get together to report their discovery studies on drug adverse problems or solutions of medication with aim to improve health care in Asia. A list of these participants and the title of their reports is shown in page 130-131, while abstracts of their report could also be found in this issue. This meeting is organized and hosted by the Department of Pharmacology and Pharmacy of the University of Hong Kong with the support from the Chinese Pharmaceutical Association, the Hong Kong Pharmaceutical Society and the International Society for Pharmacoepidemiology. Hence, it will certainly be a big event for all pharmaceutical professions in Hong Kong.

Although most therapeutics in use today have gone through premarketing study usually involves a few thousands of patients, it has been found that it is not a reliable tool to discover uncommon effects of a drug. A recent example was the worldwide withdrawal of a synthetic antibacterial fluoroqunolone derivative, temafloxacin, following postmarketing detection of hemolytic anaemia and other serious adverse reaction.[2,3] As defined by the medical faculty of Johns Hopkins University in Maryland, pharmacoepidemiology is the study of the utilization and effects of drugs in large numbers of people; it provides an estimate of the probability of beneficial effects of a drug in a population and the probability of adverse effects. It can be called a bridge science spanning both clinical pharmacology and epidemiology. Pharmacoepidemiology concentrates on clinical patient outcomes from therapeutics by using methods of clinical epidemiology and applying them to understanding the determinants of beneficial and adverse drug effects, effects of genetic variation on drug effect, duration-response relationships, clinical effects of drug-drug interactions, and the effects of medication non-adherence. Pharmacovigilance is a part of pharmacoepidemiology that involves continual monitoring, in a population, for unwanted effects and other safety concerns arising in drugs that are already on the market. Pharmacoepidemiology sometimes also involves the conduct and evaluation of programmatic efforts to improve medication use on a population basis.[4]

In this issue, we have paid some efforts to solicit recent cases of drug adverse effects or decisions made by the regulatory authorities in oversea countries. It was without difficulty that many cases were identified. Readers can get a glimpse of a few selected cases in the News & Communication Section of this issue (p.99-103) and obtain the details through source of information provided. Amongst the selected items, this editorial would like to draw our readers' attention to an important announcement made by the Canadian Authority on the availability and conditions of use of calcitonin. In the past, products contain calcitonin was regarded as a safe medication and has been used for long time to treat osteoporosis in postmenopausal women. Yet only after a more scientific study, it is discovered that prolonged and excessive medication with products containing calcitonin for symptomatic Paget's disease can cause cancer. Hence, it is not recommended for prolong use and should be kept to the minimum effective dose if no alternative choice available (p101). A paralleled important effect is the allergic response due to simultaneous use of different drugs, which may have advantages as well as disadvantages depending on their overall effect. Kwok and Mak reviewed some new evidences available and pointed out that cross sensitivity due to medication of different classes of drug should not be ignored. For more details about cross sensitivity reaction of different classes of drug, one should refer to page 107-114.

As with many western pharmaceuticals, some herbal remedies have risk associated with their use.[5,6] The fact that a botanical is completely natural does not necessarily make the use of botanical substance risk-free. Several botanicals, when consumed in their most natural form, can cause grave illness or even death in humans and animals. Although many of these botanical substances are routinely avoided by herbalists, scientists, and the general public because of their risks, yet hundreds of herbs and alternative medicines exist, and most of which have not been studied adequately, particularly in relation to their toxicology. A large retrospective study of admissions to the casualty department of a Taiwanese hospital found that 4% of admissions were related to herbal drug use, ranking herbal remedies third among drug categories most responsible for adverse effects. Nevertheless, over reaction to the presence of some toxic components in Chinese medicines is unnecessary. As it is pointed out by some experts that excessive amount of a toxicant in some Chinese medicines is either a tactic to combat a disease or a misunderstood of its effect. Many western drugs, in particular, chemotherapy drugs, are extremely toxic yet they are still in use as long as they are used under proper monitoring by a doctor. For more details of this discussion, readers are encouraged to read an article written by Lo and Cheung in page 120-123.

False claim of effectiveness, whether deliberately or unconsciously, is another matter deserves people as well as the regulatory authority's attention. Although it may not do immediate harm to a patient, it is an economic lost, and may deprive the right of receiving an expected effect or a proper treatment for the person. Tong reported that addition of Coenzyme Q10 into topical hand skin preparation failed to enhance skin barrier function in comparison to that of a placebo (page 116-119). Although the study was far from perfect and has many rooms for further improved, it does review that inadequate or inappropriate dissemination of information to the public, combined with poor study or weak regulation, can lead unwary consumers to use these products that can cause dangerous adverse reactions. Manufacturers and dealers of dietary supplements and herbal medicines spend millions of dollars each year on advertising their products. Existing regulations for product labeling of diet or herbal supplements fail to provide ample warning of risks to consumers. Indeed, many advertisements could be considered misleading or at least of questionable accuracy, despite regulatory authority has limited their claims only to proper health maintenance.


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Cheung Hon-Yeung
*Editor-in-Chief*
*16th October, 2013*

# SUCRATE® gel

(Sucralfate 1g/5ml)

## Actively treat GERD & Gastritis with lesser early relapse
## Heal damaged G.I. lesions & promote complete recovery

**Indication**
Gastro-esophageal reflux disease (GERD), gastritis and peptic ulcers of various origin

**Composition**
Per 5ml sachet containing 1 gram of sucralfate gel

**Product mechanism and features**
Not offered by any Proton Pump Inhibitors, H2-blockers or other acid suppressing agents, Sucrate Gel uniquely forms a cyto-protective layer on the inflamed and damaged mucosae of the G.I. tract. This layer prevents stomach acid, pepsin and bile salts from further eroding the ulcerated tissues. Also, Sucrate Gel stimulates the production of endogenous tissue growth factors (epidermal growth factor, fibroblast growth factor, transforming growth factor alpha, platelet derived growth factor), which promote cell regeneration and angiogenesis.

Active ulcer healing is achieved through better reconstruction of mucosal architecture and thus prevents early relapse.

- Patented gel form with double surface area of bio-adhesion to ulcerated G.I. tissues
- Does not affect acid secretion - no influence on digestion and micro-organism killing in the stomach (especially relevant for the weak elderly)
- Easily swallowed with good tolerance

**Dosage**
One sachet 2-4 times a day, according to physician's judgement.

**Manufacturer & origin**
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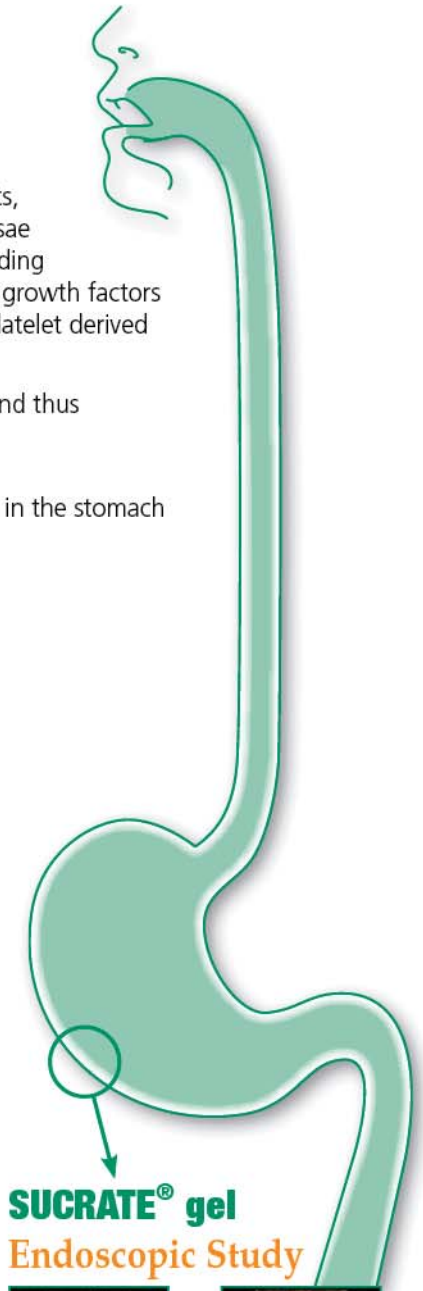


Cosentino F. et al., Società Italiana di Endoscopia Digestiva, VII Simp. Naz, Napoli, 1992


**Reference**
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4. Effect of sucralfate gel or suspension in the treatment of upper gastro-intestinal tract lesions: a controlled single-blind study. University of Pittsburgh School of Medicine


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# Boxed Warning on Increased Mortality and Severe Renal Injury and Risk of Bleeding on the Use of Hydroxyethyl Starch Solutions

**Date: June 25, 2013**

FDA has analyzed recent data that indicate an increased risk of (i) mortality and renal injury requiring renal replacement therapy in critically ill adult patients, including patients with sepsis and those admitted to the ICU; and (ii) excess bleeding particularly in patients undergoing open heart surgery in association with cardiopulmonary bypass. FDA has concluded that Hydroxyethyl Starch (HES) solutions should not be used in critically ill adult patients, including patients with sepsis and those admitted to the ICU, and a Boxed Warning to include the risk of mortality and severe renal injury is warranted. In addition, FDA has reviewed a meta-analysis of studies conducted in patients undergoing open heart surgery in association with cardiopulmonary bypass and has determined that an additional warning about excessive bleeding is needed in the Warnings and Precautions Section of the package insert.

Source: http://www.fda.gov/../ucm358349.htm?source=govdelivery

# Updates on the Use of Codeine: Restrictions on Use of Codeine for Pain Relief in Children

**Date: June 29, 2013**

A review was conducted by the EMA (European Medicines Agency)'s Pharmacovigilance Risk Assessment Committee (PRAC), which investigated reports of serious and fatal respiratory depression in children after taking codeine for pain relief. Most of the cases occurred after surgical removal of the tonsils or adenoids for obstructive sleep apnoea (frequent interruption of breathing during sleep). The PRAC concluded that a number of risk minimisation measures are necessary to ensure that only children for whom the benefits are greater than the risks are given the medicine for pain relief. The risk of side effects with codeine may also apply to adults. Codeine should therefore not be used in people of any age who are known to be ultra-rapid metabolisers nor in breastfeeding mothers.

The United Kingdom: MHRA confirmed that codeine-containing medicines should only be used in children over 12 years old to treat acute (short lived) moderate pain, and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen. Where it is used in children it should be used at the lowest effective dose and only for the shortest period of time recommended by the doctor. This is because some patients may be at an increased risk of rare but serious adverse reactions as a result of the way the body handles codeine and younger children may be particularly susceptible. It has also been concluded that codeine should not be used at all in any patient under 18 years old who undergoes the removal of tonsils or adenoids for the treatment of sleep apnoea. This is due to an increased risk of severe breathing difficulties.

Source: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON287048

Source: http://www.ema.europa.eu/../news_detail_001829.jsp&mid=WC0b01ac058004d5c1

# Updates on the Use of Diclofenac

**Date: June 29, 2013**

The MHRA confirmed that patients with serious underlying heart conditions, such as heart failure, heart disease, circulatory problems or a previous heart attack or stroke should no longer use diclofenac, This follows completion of a European review which found a small increased risk of heart attack and stroke. Dr. Sarah Branch, Deputy Director of the MHRA's Vigilance and Risk Management of Medicines Division said: "Whilst this is a known risk and warnings have been included in patient and healthcare information for some time, this advice is now being updated. For many patients diclofenac will continue to provide safe and effective pain relief but is no longer suitable for certain at risk groups. Those with underlying heart conditions currently taking diclofenac should speak to their GP or pharmacist at their next routine visit to consider an alternative pain relief treatment. Patients with certain cardiovascular risk factors such as high blood pressure, raised cholesterol, diabetes and smoking should only use diclofenac after careful consideration with their GP or pharmacist."

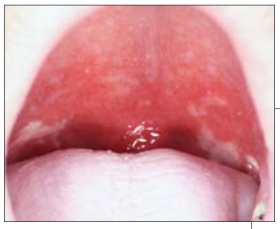
Source: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON287042

Management of the

# SIDE EFFECT resulting from Chemotherapy / Radiotherapy

## Chemotherapy / Radiotherapy

- Compromise patients' immune system.
- Lead to oral inflammation[1,2]
  - Mucous membrane shredding



## Poor Oral Hygiene Negatively
impacts Chemotherapy / Radiotherapy

- Disrupt cancer therapy[4]
- Impose potential source of life-threatening systemic infections[3]
- Affect patient quality of life[4,5]


## Povidone-Iodine (BETADINE) Gargle & Mouthwash helps manage Oral Inflammation[6]

- Reduce the incidence, severity and duration of radiation-induced oral inflammation
- Delay the onset of oral inflammation
- Speed-up recovery from oral-mucositis by as much as 45 days ($p<0.001$)

## BETADINE Gargle & Mouthwash contains PVP-I

- Reduces the risk of developing serious oral inflammation by 70% ($p<0.005$)[6]
- Help relieve the oral inflammation symptoms
- Possess broad spectrum killing power against bacteria, viruses and fungi[7]

| G+ | G– | Spores | Fungi | Virus |
|---|---|---|---|---|
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**BETADINE® Gargle and Mouth Wash - ABRIDGED PRODUCT INFORMATION**
**Composition:** Povidone-iodine **Indications:** Symptomatic relief of inflammatory conditions of the mouth and pharynx, including stomatitis, gingivitis, aphthous ulcers, pharyngitis, tonsillitis, monilial infections, and sore throat due to common colds and influenza. As a prophylactic during and after surgery e.g. after tonsillectomy and dental procedures. Acutine use to promote oral hygiene. **Dosage and Administration:** Use undiluted or diluted with two parts of water for 30 sec, repeat up to 4 times daily if needed. Existing lesions: Rinse for 2 minutes, up to 4 times a day especially after meals. **Contraindications:** Known hypersensitivity to iodine, hyperthyroidism, before and after radioiodine therapy, thyroid carcinoma, goitre or following thyroid diseases, concomitant lithium therapy. Children under 6 years old. Pregnancy and lactation. **Precautions:** Remove false teeth, braces etc. from the mouth before using the product to avoid discolouration. **Adverse Reaction:** hypersensitive skin reactions, Systemic: metabolic acidosis, hypematraemia, impairment of renal function, iodine-induced hyperthyroidism. **Interactions:** Wound treatment preparation containing enzymes, hydrogen peroxide, taurolidine, diagnostic agents with toluidine or gum guaiac. **Presentation:** Gargle/mouthwash 1% x 250 mL.
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# Canada: Important Changes to the Availability and Conditions of Use for Drugs Containing Calcitonin

**Date: August 1, 2013**

Health Canada is informing Canadians of important changes to the availability and recommended conditions of use of drugs containing calcitonin. Calcitonin is used as a nasal spray to treat osteoporosis (loss of calcium in bones) in postmenopausal women and as an injection to treat Paget's disease (a chronic bone disorder) and hypercalcemia (high blood calcium).

A safety review conducted by Health Canada has concluded that there is a slightly increased risk of cancer associated with the prolonged use of calcitonin products. A review of the benefits and risks of the nasal spray products found that there was not enough evidence of benefit to continue using calcitonin nasal sprays in treating osteoporosis, given the increased risk of cancer. As a result of these reviews, calcitonin nasal spray products will no longer be authorized for sale in Canada as of October 1, 2013. This transition period will allow patients using calcitonin nasal spray to be transferred to other treatments.

Calcitonin injectable products will continue to be authorized for sale in Canada. The benefits of these products are considered to outweigh the risks when the product is used as directed in the Product Monograph (i.e., for Paget's disease and hypercalcemia). However, the labels for calcitonin injectable products are being updated to include a new warning about this risk, and to recommend that treatment with calcitonin solution for injection be limited to the shortest possible time, using the minimum effective dose. Treatment of symptomatic Paget's disease with calcitonin medicine should be limited to patients who are unable to use other treatments. Patients who are taking a calcitonin medicine and who have questions should speak to their healthcare practitioner before making any change to their treatment. There are other medications authorized in Canada for the treatment of osteoporosis, Paget's disease and hypercalcemia. Patients should speak to their pharmacist regarding the safe disposal of calcitonin nasal spray products.

Source: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/../34843a-eng.php

# Increased Glucose Level May Increase the Risk of Dementia

**Date: August 8, 2013**

Studies have found that, not only diabetes is a risk factor for dementia, higher glucose levels may also increase the risk of dementia in people without diabetes. In an observational study involving 2067 participants without dementia to examine the relationship between glucose levels and the risk of dementia. During a median follow-up of 6.8 years, 524 participants developed dementia (74 with diabetes and 450 without). Among the participants without diabetes, higher average glucose levels within the preceding 5 years were related to an increased risk of dementia (P = 0.01); with a glucose level of 115 mg/dL (6.4 mmol/L), as compared to 100 mg/dL (5.5 mmol/L) in the group without developing dementia, the adjusted hazard ratio for dementia was 1.18 (95% confidence interval [CI], 1.04 to 1.33). On the other hand, among the participants with diabetes, higher average glucose levels were also related to an increased risk of dementia (P = 0.002); with a glucose level of 190 mg.dL (10.5 mmol.L), as compared to 160 mg/dL (8.9 mmol/L), the adjusted hazard ratio was 1.40 (95% CI, 1.12 to 1.76). The study suggested that higher glucose levels may associate with a higher risk for dementia.

Source: New England Journal of Medicine

# Singapore: Potential Interaction between Warfarin and Health Supplements Containing Vitamin K

**Date: August 30, 2013**

Healthcare professionals are reminded to be aware of a potential interaction between warfarin and health supplements containing vitamin K. A local adverse event report was received from a doctor involving an 80-year-old patient on long-term warfarin therapy and concurrent use of Centrum Silver®. The patient, who was a long-term user of Centrum Silver®, had been on the same warfarin dose for the past three years with International Normalised Ratio (INR) within the therapeutic range. During a routine blood test, the INR was unexpectedly reduced to a sub-therapeutic level. Further investigations revealed that the Centrum Silver® taken by the patient was a new formulation with an additional 25mcg of vitamin K1, which was not present in the earlier formulation. Small amounts of vitamin K1 (e.g., 10-25mcg) contained in multivitamin supplements are generally considered safe in patients undergoing warfarin anticoagulation therapy. Healthcare professionals managing patients on warfarin are encouraged to monitor their patients' INRs and counsel them on their vitamin K intake from health supplements and food.

Source: http://www.hsa.gov.sg/publish/hsaportal/../potential_interaction.html

# New Partner State Key Laboratory Pushes Frontiers in Metabolic Medicine

**Date: September 2, 2013**

In a strategic collaboration between the University of Hong Kong and Nanjing University, a new Partner State Key Laboratory of Pharmaceutical Biotechnology has now been established at the Li Ka Shing Faculty of Medicine. The Chinese Ministry of Science and Technology granted official approval for the laboratory in early July this year. The Laboratory will strengthen research ties between scientists on the Mainland and in Hong Kong. It is the fifth State Key Laboratory to be set up at The University of Hong Kong. State Key Laboratories are seen as hubs for research excellence and significantly contribute to China's development in science and technology. In addition to research collaboration, they also facilitate academic exchange between China and the overseas scientific community.

Led by Professor Aimin Xu at the Department of Pharmacology and Pharmacy, and the Department of Medicine, the State Key Laboratory for Pharmaceutical Biotechnology will carry out vital research on metabolic medicine, with particular emphasis on obesity, diabetes and the associated complications. Professor Ian Wong, Head of Department of Pharmacology and Pharmacy, said the Key State Laboratory is extremely important for the pharmacy profession in Hong Kong and China. He said pharmacists' unique skills are essential to the development of appropriate formulations for new drug molecules. The State Key Laboratory will also apply state-of-the-art pharmaceutical technology to "pharmaceutical translational research" to develop formulations for existing drug molecules, he added. "The immediate implication is that we can build a long term and sustainable platform for our research," said Xu, "It's the first such laboratory to focus on metabolic medicine."

Currently, Xu is exploring the potential for adipokines to be used as diagnostic markers for the early prediction of diabetes and diabetic complications; and as a therapeutic target to develop a cure for diabetes. "We have many anti-diabetic drugs available but none can cure the disease, simply because we do not know the early pathogenesis. Adipokines can be used as an early bio-marker and also as a therapeutic target for early intervention," Xu says.

A significant challenge for diabetic management in China, as with many developing countries, is that over 50% of people with diabetes are not diagnosed until complications set in. "Once you have diabetic complications it's too late," says Xu. Raised blood glucose levels are a late indication so the search is underway for an assay for early diagnosis or even risk prediction of diabetes.

There is stiff competition. Xu and his team are not the only ones after the Holy Grail of a cure for diabetes. "But, we are the leading group in the world," he said proudly, "We have discovered several new adipokines, originally discovered in our laboratory." To date, they have developed a wide range of assay kits for diagnosis. A number of these are currently used in clinical trials and every effort is being made to get a further two to the clinical trial stage in China. Xu cites an example in Australia where one of their assay kits is being used in an anti-lipid clinical trial of over 20 000 subjects.

Xu's view is that biomarkers will become a key component in personalised diabetic management. "Although all diabetic patients have hyperglycaemia, each patient is different, they have different genetic and environmental factors which contribute to its development, so it's very important in the future to have these personalised," he said.

Source:http://www.med.hku.hk/v1/press-releases/partner-state-key-laboratory-of-pharmaceutical-biotechnology-opened-at-hku/

# Canada: Association of Sutent (sunitinib malate) with Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

**Date: September 7, 2013**

Pfizer Canada Inc., in collaboration with Health Canada, has informed healthcare professionals and the public of an important revision to the Product Monograph, including the consumer information section, for Sutent (sunitinib malate).

According to Health Canada, Sutent is indicated for the treatment of gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance. It is also indicated for the treatment of metastatic renal cell carcinoma (MRCC) of clear cell histology and for the treatment of patients with unresectable locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumours (pancreatic NET), whose disease is progressive. A statement has been recently added to the Canadian Product Monograph to inform healthcare professionals and patients about a potential association between the use of Sutent and severe cutaneous reactions suggestive of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Early recognition is important in improving prognosis. Cases of Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), including fatal cases, have been very rarely reported, mostly in the post-marketing setting, in patients who have used Sutent. Health Canada advised healthcare professionals that if signs or symptoms of SJS or TEN are present, Sutent treatment should be discontinued; and if the diagnosis of SJS or TEN is confirmed, treatment must not be restarted. The Canadian Product Monograph has been updated to reflect this risk.

The potential risk of the cutaneous adverse events of Toxic Epidermal Necrolysis (TEN), and Stevens-Johnson Syndrome (SJS), with sunitinib use was evaluated using a review of currently available safety data from published literature, the Pfizer global safety database containing clinical trial serious adverse events and post-marketing reports, the US FDA Adverse Event Reporting System (AERS) database, and the Canada Vigilance database. Out of an estimated 214,848 patients exposed to sunitinib between 26 January 2006 and 30 April 2013, there were 4 reported cases of TEN and 5 reported cases of SJS internationally, although diagnosis was not confirmed in all cases. Two of the potential TEN cases had fatal outcomes. There have been no Canadian cases reported as of 30 April 2013.

Source: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/../35473a-eng.php

# Hong Kong Pharmacist Won the 2013 Royal Pharmaceutical Society Leadership Award Recognizing Work in Elderly Homes Medicines Safety

**Date: September 9, 2013**

The 2013 Royal Pharmaceutical Society (RPS) awards were presented last night at a gala dinner at the RPS Conference to celebrate the achievements of teams and individuals within the Pharmacy profession. Mr. Peter Suen, Chief Pharmacist of Active Care Pharmacy, Hong Kong won the RPS Leadership in Pharmacy Award, which recognized his work in Old Age Homes medication management in Hong Kong. Over 350 guests cheered the finalist and eight award winners whose excellence and innovation in improving and enhancing patient care proved truly outstanding. The awards encompass all sectors within the profession and range across all career stages, from Student of the Year to our Lifetime Achievement Award.

RPS Chief Executive Helen Gordon said: "Huge congratulations to all of our finalists and award winners. I'm delighted the achievements of members have been recognised by our annual awards programme. The innovative and proactive approach they demonstrate towards improving patient care is genuinely inspiring."

Mr. Peter Suen said: "The work in Old Age Homes medication management was initiated by the Pharmaceutical Society of Hong Kong under the leadership of Mr. Benjamin Kwong and continuously supported by Mrs. Mary Cheng and members of the General Council over the years." In Hong Kong, because of a shortage of nursing and pharmaceutically trained staff, some nursing homes allowed unqualified workers to prepare and administer medicines. There is a need to develop a training course for the unqualified nursing home workers and to develop a medication management systems and guidelines to allow appropriate systems to be implemented in nursing homes. Mr. Peter Suen, in partnership with the Pharmaceutical Society of Hong Kong and the Caritas Institute of Higher Education, took the initiative to develop a course, involving 99 hours of teaching and practical part time study for nursing home workers. Based on the initial software used by the Pharmaceutical Society of Hong Kong, he invested in the development of a new bilingual data medication management system allowing web-based management with ISO 9001 certification. He also applied for a grant from the Hong Kong government's trade and industrial department to pilot an implementation study of a medication management system. The system is now suitable for the use of Hong Kong nursing homes and helps prevent medication administration errors in the nursing homes. Professor Ian Wong, Head of Department of Pharmacology and Pharmacy of the Hong Kong University, nominated Mr. Peter Suen. He said "Peter Suen has expanded substantial effort to improve the use of medicines in nursing homes. He has been a leader who is able to work with the professional body, the care providers and the government's social welfare department to improve pharmaceutical care of the elderly in Hong Kong."

Open to any sector, this will be awarded to those who have shown leadership within pharmacy, whether that be industrial developing a new process, hospital delivering an innovative service, community selling the benefits of pharmacy above and beyond, academia for a new research paper or novel teaching process, primary care for innovative ways of working.

Source: http://www.rpharms.com/home/home.asp
and www.pjonline.com

Peter Suen(left) and Stephen Howard, FRPharmS, superintendent pharmacist at Lloyds pharmacy who presented the award

# Erratum for Volume 20(1) January- March, 2013

There is a printing error on page 21 for Table 2 in the "Overview of Targeted Therapies for Renal Cell Carcinoma"

For T3+N0 or N1 disease, the disease staging should be in Stage III instead of Stage IV. Correct Table 2 as below:

**Table 2. AJCC TNM Staging System for kidney cancer. [Adapted from Edge, et al][23]**

| Primary Tumor (T) | | | Regional Lymph Nodes (N) | | | |
|---|---|---|---|---|---|---|
| | **Involvement** | **Extent of disease** | NX | Regional lymph nodes cannot be assessed | | |
| TX | Primary tumor cannot be assessed | | N0 | No regional lymph node metastasis | | |
| T0 | No evidence of primary tumor lymph node(s) | | N1 | Metastasis in a single regional | | |
| T1a | Tumor ≤ 4 cm | limited to kidney | **Distant Metastasis (M)** | | | |
| T1b | Tumor ≥ 4 cm to ≤ 7 cm | | M0 | No Distant Metastasis | | |
| T2a | Tumor >7cm to ≤ 10cm | | M1 | Distant Metastasis | | |
| T2b | Tumor > 10 cm | | **Staging** | | | |
| T3a | Into renal vein or its segmental branches | not beyond Gerota's fascia | Stage I | T1 | N0 | M0 |
| T3b | into vena cava | below the diaphragm | Stage II | T2 | N0 | M0 |
| T3c | Into vena cava or invades wall of vena cava | above the diaphragm | Stage III | T1 or T2 | N1 | M0 |
| | | | | T3 | N0 or N1 | M0 |
| T4 | invades beyond Gerota's fascia | Including contiguous extension into the ipsilateral adrenal gland | Stage IV | T4 | Any N | M0 |
| | | | | Any T | Any N | M1 |

# A Community Pharmacist Can Make a Difference - An Interview with Anita Chan

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## INTRODUCTION

Anita Chan shares her career path and role as a community pharmacist at the Philanthropic Community Pharmacy of St. James' Settlement.

### Background

*Ms. Anita Chan*

After gaining her Pharmacy undergraduate degree in the US, Anita decided not to study medicine as intended. Instead, she began her career in a community pharmacy where she met her first mentor. During this period she was deeply impressed by how her mentor showed wholehearted care during patient counseling despite the concept of pharmaceutical counseling was not prevalent at that time. This made a huge impact on Anita's career as a community pharmacist.

After nine-year of practice in two chain pharmacies, Anita joined Walmart in Chicago and managed a new niche of pharmacy business – operation of a community pharmacy at a warehouse store that targeted the upper middle-class. She began to involve in more customer service and business operation work. Through establishing strong customer relationship and providing good patient counseling service, the value of the warehouse pharmacy became recognized over time. Six years later Anita progressed to another position in Walmart in California, where she became the Director of Operation. She oversaw the operations of pharmacy in 4 different states and managed the human resources of the pharmacy including recruiting and retaining pharmacists. In addition, she was involved in the management of profit-generating and image building of the pharmacy.

After 20 years of living in the US, Anita decided to move back to her roots - Hong Kong, with her families in 2009, hoping that her children can learn about the traditional Chinese culture and receive education in Hong Kong. At the beginning, Anita expected to start her career from scratch. She embarked on working as a community pharmacist in a chain pharmacy. Soon thereafter she resigned from the job and joined St. James' Settlement (SJS) where she helped found the Philanthropic Community Pharmacy - the first nonprofit community pharmacy in Hong Kong.

**PJ: Why did you choose to join St. James' Settlement?**

**Anita:** In fact, I didn't plan what to do when I came back to Hong Kong. I knew that I have to start everything from scratch like a fresh graduate. At the time I joined SJS, I just knew it's a NGO (non-governmental organization) that was planning to set up a nonprofit community pharmacy. So I thought my past experience of establishing new community pharmacy in the business sector might help in this aspect. Therefore, I decided to give this a try.

**PJ: What are the criteria when determining the target service group of different projects?**

**Anita:** Unlike my previous job, I am lucky that I do not have to worry too much about the profit of the pharmacy now. Our goal is to help as many people as possible to receive

appropriate treatment. There is a very clear goal when we set up the pharmacy: all patients should have the chance to receive appropriate treatment regardless of their background (病者有其藥). Patients with financial burden should not receive an inferior treatment or bear more side effects. Besides, I am grateful to have the support from SJS which allows me to promote the role of a community pharmacist - our second goal of running the pharmacy. Together with our dispenser, we hope to let the public recognize the role of a community pharmacist and dispenser in drug education and help them acquire proper knowledge of taking drugs (知藥用藥). We do not just instruct the patients on how to take the drugs; we make sure they are taking the drugs correctly. For example, we use a cardboard with cartoons of a sun and a moon to illustrate the administration time for illiterate elderly.

**PJ: How do you gain support from the pharmaceutical companies?**

**Anita:** At the beginning, there was a huge resistance from the pharmaceutical companies. They did not see the point in selling the drugs to us at a lower price, and were concerned about the negative feedback from physicians and other community pharmacies. Fortunately, they gradually perceived the positive value of our work. They realized that patients who are in need can really benefit from getting the drug through our service, and this has fulfilled their corporate social responsibility. Moreover, the program provides physicians with an option to choose new expensive drug for suitable patients who are not able to pay for the drug out of their own pocket. This group of patients can acquire their needed medications at a much affordable price or even free at times, which can largely improve their health outcome and quality of life. After all, with more physicians willing to prescribe new drugs and more patients being able to benefit from this, pharmaceutical companies become more supportive to our program.

**PJ: Does your previous work experience in the US help your job at present?**

**Anita:** Definitely yes. Although discrimination in the US is very uncommon, I unfortunately had a bad experience with my store manager in my previous workplace. He was a 6'5'' tall man who came from New York. He disliked Asian people and was not happy about the high salary of pharmacist. Initially, we were in a very hostile relationship. He would threaten me with words when things went wrong in the pharmacy. But then I realized that communication and mutual understanding were the keys to solve the conflict. I shall look at things from his point of view and show him what a pharmacist is actually doing everyday and how we contribute to generating income for the store. I might also join the manager meeting to assist development of the store. I learned a lesson from this experience that I can apply to the relationship between healthcare professionals and patients. There shouldn't be a hierarchy between pharmacists and patients. We shall communicate with patients in an equal position. Having this in mind, we have created an environment in the pharmacy that facilitates mutual communication.

**PJ: Can you share with us the things that you feel happy or unhappy about with your current job?**

**Anita:** To be honest, I am really happy and satisfied with my job. I gain different learning every day, and I have many chances to try out a variety of things, for example, writing newspaper articles and participating in radio program about drug education.

Besides, I am so glad to meet different pharmacy students as I can share my experience with them. It's so nice to see our future pharmacists having such a good academic background and I am sure that they will continue contributing to our pharmacy society.

**PJ: Do you feel discouraged when you see patients unable to afford the drugs?**

**Anita:** Yes, I do feel sorry about this. But I'd see things in a different way – I am an optimistic person; I'd take it as an opportunity for me to reflect on myself and treasure people around me and things that I have. We will do our best to help all patients who come to our pharmacy.

**PJ: What is most rewarding about your job at SJS?**

**Anita:** First of all, working at SJS allows me to have learning every day, for example, I learned about the job of a social worker and the operation of a NGO, etc. Second of all, I am happy to receive positive feedbacks from the patients. It is such a great job satisfaction to me. Through applying my drug knowledge in communicating with patients, it can really have a noticeable impact on their healthcare.

I feel blessed that I have the ability to help those who are deprived and underprivileged.

Another thing is that - many people think that community pharmacists do not have much opportunity to use their clinical knowledge. But in fact, there are plenty of opportunities to use your clinical skills in community pharmacy setting, for example we need to know at what glucose level/blood pressure level we should contact the physician, etc. Therefore, community pharmacists also need to be well-equipped with clinical knowledge.

Besides, I am delighted to collaborate with our dispenser who assists in patient education through conducting visits to the patient's home. This facilitates us to address the actual need of the patient. It also enables every one of us to use our skills and knowledge to our greatest potential.

**PJ: Have you encountered any challenges at work?**

**Anita:** Yes, one of the challenges is that people don't understand the role of a pharmacist. Patients who are

going to purchase their medication at our pharmacy need to make an appointment first. So that we can have a proper counseling with them that usually lasts for 15-20 minutes. However, some patients dislike and complain about the booking procedure because they just want to get the drugs as early as possible and they don't realize the importance of medication counseling. To deal with this, I need to help them understand the operation and mission of our pharmacy and recognize the role of a pharmacist.

The second challenge comes from gaining support from the pharmaceutical companies that I mentioned previously.

**PJ: Have you come across any memorable cases?**

**Anita:** There are indeed a lot of memorable cases. I particularly remember an old lady who has hypertension – she really appreciates our help and calls us for assistance over time. We have built a genuine relationship that she is like a good friend to all of us now. One of the reasons is that we do not only concern about the physiological problem of the patient, we also care about their inner needs, which is in fact one of our major objectives.

There is another patient who suffered from liver cancer. Unfortunately he has passed away already. It was sad that he progressed from hepatitis B to liver cancer because he was not able to afford the medications for treatment of hepatitis B at earlier stage. Before he left, he told us that he always recalled our words of encouragement ("Be strong! We support you.") during tough times. I never thought that our small action can have such a meaningful impact on patients.

**PJ: What is the future direction of development of Philanthropic Community Pharmacy?**

**Anita:** We hope to expand our pharmacy services. We'd like to have more collaboration with different parties, for example to maximize the role of dispensers in drug education.

**PJ: What is your personal plan for future?**

**Anita:** I hope that I can continue helping more people in different classes.

**PJ: What advice would you offer to a newly registered pharmacist?**

**Anita:** Do your job with your heart, no matter which sector you are working in. Do not just focus on money. Money is only a short-term target that shouldn't be your first priority. You should find a job you love and enjoy doing. People can definitely feel your enthusiasm and appreciate your positive attitude towards your job. Last but not least, I want to point out that community pharmacists also have lots of opportunities to apply their clinical knowledge. A pharmacist should not limit their career to hospital pharmacy only.

**PJ: Do you have anything that you'd like to share with the readers?**

**Anita:** I am so happy to come back to Hong Kong where I can attempt and try out different things in a completely flexible and new approach. Lastly, I just want to say - no matter which country or which sector you are working in, you can still achieve your goal if you do your job with your heart.

## CONCLUSION

Attitude is a little thing; but it can make a big difference. Anita has shown us that a community pharmacist can really make an impact on people's healthcare and quality of life.

## REMARK

Anita Chan, at the point of publication of this interview, has departed from her role at St. Jame's Settlement. She is currently the Medical Affairs Manager at Pfizer Hong Kong.

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# Cross Sensitivity Reaction of Different Drug Classes

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**ABSTRACT**

**Allergic reaction is a common drug-related problem. Cross sensitivity between different drug classes has been debatable with the emerging new evidence available. Knowledge about cross sensitivity is very important in clinical setting as it will greatly affect the choice of drugs. This article discusses cross sensitivity between different drug classes including Penicillin and Cephalosporin, Penicillin and Carbapenem, Sulfa drugs, Non-steroidal anti-inflammatory drugs (NSAID) and Anti-convulsants. The difference in the mechanism of action, different types of hypersensitivity reactions and how the chemical structures of the drugs affect the cross sensitivity are also discussed.**

***Keywords:*** *Cross sensitivity, hypersensitivity reaction, antibiotics, anti-convulsants, NSAID*

## INTRODUCTION

Allergic drug reaction is not uncommon. It accounts for 5% to 20% of all cases of adverse drug reaction.[1-4] The Hospital Authority has taken the lead to prevent allergic drug reactions by implementing various measures. Drug allergies and histories column on the Medication Administration Record (MAR) and the drug allergy module in the Clinical Management System (CMS) are useful tools to allow proper documentation of drug allergy history about the presentation and the time of occurrence. Better documentation of drug allergies and histories can alert clinicians to the risk of allergic drug reaction when agents within the same drug class are being used.

Allergic drug reactions can be classified into four types based on their immunological responses. Type I allergic drug reactions are anaphylactic reactions. It describes a process in which drug-hapten reacts with IgE antibody on the surface of mast cells and basophils. This process causes the release of mediators to trigger immunological response. The clinical manifestation of this type of reaction ranges from pruritus to circulatory collapse and death. Anaphylactic reactions to antibiotics and radiographic contrast media occur in 1 in every 5,000 exposures with 10% mortality.[5]

Type II reactions are cytotoxic reactions which involve IgG or IgM mediated reactions through different mechanisms. Common clinical manifestations of this type of reactions include hemolytic anemia, thrombocytopenia and granulocytopenia. Type III reactions are immune-complex-mediated reactions, which are triggered by the formation of drug-antibody complexes in serum which often deposit in blood vessel walls and subsequently activate complement and endothelial cell injury.[5] This type of reactions is sometimes referred to as serum sickness, with symptoms of fever, urticaria and lymphadenopathy 7 to 21 days after exposure.[6-7] Type IV is the cell-mediated (delayed) reactions. It involves direct activation of T cell-mediated reaction by the drug. It often manifests as delayed type of contact dermatitis with the distinct patterns of cytokine release and effector-cell recruitment.

As allergic drug reactions can be categorized into different types of reactions with different mechanisms, cross sensitivity can also be anticipated and explained by these mechanisms and the structural similarity between drug groups. The mechanism and frequency of occurrence of cross sensitivity of different drug classes will be further elaborated in this article.

## PENICILLIN AND CEPHALOSPORIN

IgE hypersensitivity reactions and non-IgE hypersensitivity reactions were both proposed to explain the cross hypersensitivity reaction between penicillins and cephalosporins. IgE hypersensitivity reaction involves combination of antibiotics with a carrier protein. The beta-lactam ring opens under physiological conditions and covalently binds to a protein to form an antigenic determinant. Penicillyoyl-determinant is one of the major type of determinants which contributes to 75% of IgE mediated allergic reactions.[8] Cephalosporins with similar side chains would form a structurally similar antigenic determinant which contributes to cross sensitivity reactions of penicillins and cephalosporins with similar side chains.[9]

As shown in Figure 1, the side chains of Ampicillin and Cephalexin (a first generation cephalosporin) are the same. When the beta-lactam ring is opened and attached to a protein, the side chain will be exposed and form a determinant with similar structure. It could explain the high cross sensitivity rate between penicillins and first generation cephalosporins. While

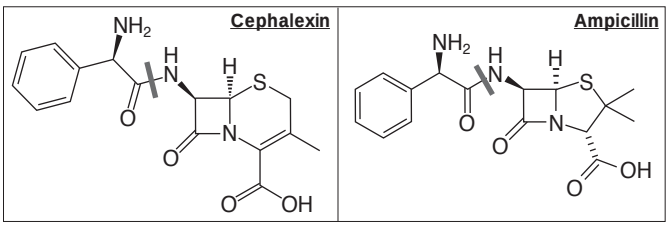


***Figure 1:*** *Structures of Ampicillin and Cephalexin*

the structural similarity of the side-chain between penicillin and first generation cephalosporin is high, that for second and third generation cephalosporin is lower. A correspondingly lower cross-sensitivity rate between penicillin and the second and third generation cephalosporin is therefore anticipated.

Back in 1970s, Dash and Petz suggested that the cross sensitivity reaction between penicillins and cephalosporins should be around 8.1% which is 4-fold higher when compared to patients without history of penicillin allergy which was considered to be around 1.9%.[10-11] The cross sensitivity rate was then quoted to be around 10%.[12] With the assumption of hapten formation and the reaction of side chains, the cross sensitivity rate between penicillins and cephalosporin is now considered to be around 0.5 – 6.5% with greater contribution from first generation cephalosporin.[16] Another possible explanation for the previously reported higher incidence of cross sensitivity between penicillins and cephalosporins is that penicillin related compound was produced by cephalosporium mold at the early stage of drug development.[17]

### Non-IgE type hypersensitivity reaction

Another proposed mechanism for drug hypersensitivity is the p-i concept (pharmacological interaction with immune receptors). It proposed that drugs can bind directly to immune receptors like T-cell receptors (TCR) by van der Waals forces, electrostatic or hydrogen bonds and present to Major Histocompatibility Complex (MHC) to trigger T cell response. Stimulation may only occur under certain circumstances, (i) the drug has a certain affinity for the particular TCR; (ii) a supplementing interaction of the TCR with the MHC molecule takes place; and (iii) the T cell is ready to react to such a minor signal given by the drug-TCR interaction.[13]

Cross sensitivity of this type applies to drug class with structural similarities and precursor frequency of drug-specific T (or B) cells. For severe and delayed hypersensitivity reaction, T-cell precursors are detectable for years after acute events.[14] Clinical symptoms arise when drug-specific T cells expand sufficiently to reach a certain number at the inflammatory site and cause inflammation. If only a small fraction of drug-specific T cells cross react and the starting precursor frequency remains low, the symptoms may be delayed. Therefore, if the causative agent is stopped early enough, no obvious symptoms may be seen. However, such interaction does not apply to IgE-mediated reactions.

Drugs which differ by only a hydroxyl group (-OH) are more cross-reactive than drugs which are different in a longer side-chain. Previous study showed T-cell clones that react with amoxicillin also react with ampicillin which differs from amoxicillin only a hydroxyl group[15] (Figure 2). No cross sensitivity was seen between these amoxicillin-specific T-cell reaction and cephalosporins.

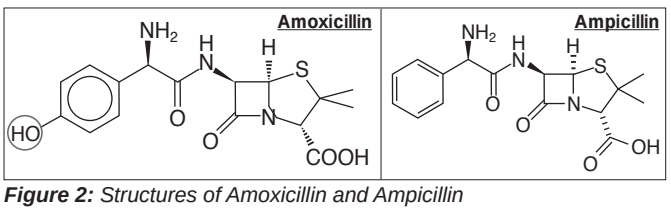


***Figure 2:*** *Structures of Amoxicillin and Ampicillin*

### PENICILLIN AND CARBAPENEM

Carbapenem group also shares the similar chemical structure as other beta-lactam antibiotics (Figure 3). Historically, it was reported to have 50% cross sensitivity of IgE reaction between penicillin and carbapenem.[36] This study involved 40 patients with documented allergic history to penicillin and 19 of them showed positive skin test to penicillin. Further skin test was performed to test the allergic reaction to imipenem by skin test. Nine of them showed positive result. Since then, 25% cross sensitivity based on skin test and 50% cross sensitivity based on history were reported. Several retrospective studies were conducted recently to estimate the cross sensitivity rate of penicillin and carbapenem, which was found to be around 9.5 – 12.2%.[37-39] An even lower rate of 0.8-0.9% was observed in prospective studies.[40-42] Patients with negative skin test tolerated subsequent challenges with carbapenem. Skin test was then recommended in clinical setting to estimate the risk of carbapenem hypersensitivity. This test, however, is not readily available in HA hospitals.

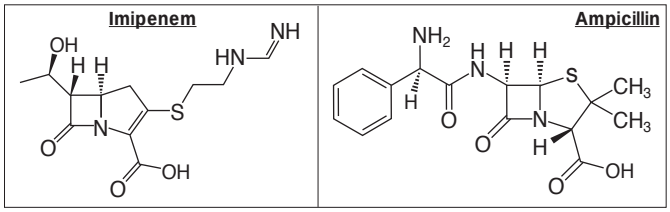


***Figure 3:*** *Structures of Imipenem and Ampicillin*

### Summary

As cross sensitivity among beta-lactam antibiotics can occur through different mechanism of actions, both structural similarity together with the type of hypersensitivity reaction should be carefully evaluated when clinical judgment has to be made.

### SULFA DRUGS

"Sulfa" allergy is a generic term used to describe allergic reaction to sulfonamide antibiotics. It does not imply allergy to compounds containing sulfur, inorganic sulfate or sulfites.[18] Sulfonamide antibiotics are derivatives of sulfanilamide.[19] The term sulfonamide is used to describe any compound with an $SO_2NH_2$ moiety regardless if it directly links to a benzene ring. Sulfonamide antibiotics are differentiated from other sulfonamide non-antimicrobials by two main features in their chemical structures. The first feature is that the amine group of the arylamine group is situated at the para position of the $SO_2NH_2$ moiety. Another characteristic is a 5- or 6- member aromatic heterocyclic ring with ≥1 nitrogen at the N1 position (as seen in the structure of sulfamethoxazone) (Figure 4).

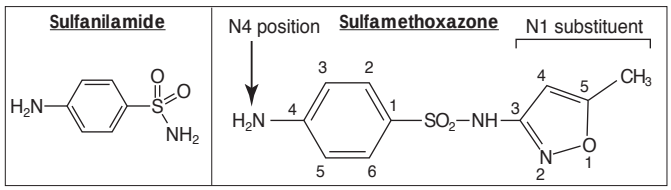


***Figure 4:*** *Structures of Sulfanilamide and Sulfamethoxazone*

Sulfonamide non-antibiotics are chemicals that contain $SO_2NH_2$ moiety without the above mentioned characteristics, for example, furosemide (Figure 5).

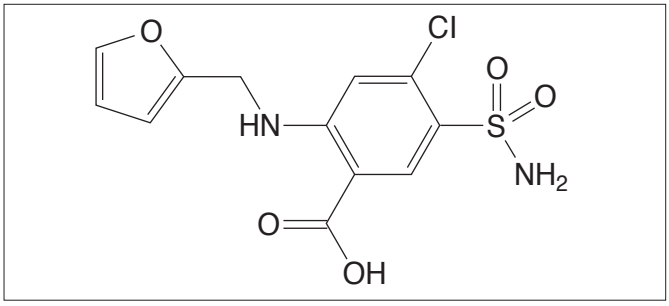


***Figure 5:*** *Structures of Furosemide*

by urine. Alternatively, it can be reduced back to the original sulfonamide hydroxylamine by intracellular glutathione. Such redox cycling occurs in many cell types including erythrocytes. Superoxide radicals produced by the repeated redox cycling cause oxidative stress and are believed to be associated with Methemoglobinemia which is non-immune, direct cytotoxicity.

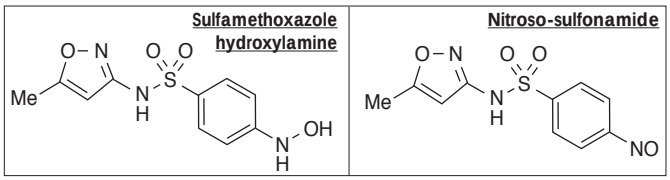


***Figure 6:*** *Structures of Sulfamethoxazole hydroxylamine and Nitroso-sulfonamide*

**IgE type hypersensitivity reaction**

Sulfonamide antibiotics can trigger all four types of immunological reactions. Previous study showed that serum IgE antibodies can be detected in patients who experienced true type I reaction to sulfonamide antibiotics.[20] Interaction between IgE and sulfonamide antibiotics is shown to be highly stereospecific and it is mediated by specific structure in the molecule. The nitrogen heterocyclic ring has been showed to be immunogenic but not the sulfonamide group. The methyl group in the beta-position of an isoxazole ring, which can be found in sulfamethoxazole only, is the most powerful determinant of IgE binding.[21-22] Furosemide (a.k.a Frusemide) does contain a sulfonamide group and is considered a drug to be avoided in patients with allergy history of sulfonamide antiobiotics.[23] However, a study in 2002 showed that serum-derived anti-sulfamethazine antibodies from allergy patients did not bind to furosemide.[24] It was concluded that cross sensitivity between furosemide and sulfonamide antibiotics is unlikely.

**Non-IgE type hypersensitivity reaction**

Non-type I reactions however may not be follow the same mechanism of action. Three possible etiologies were proposed to explain the non-type I reactions. The first possible etiology is that the parent sulfonamide antibiotic or its metabolite binds to cellular protein and causes tissue damage by direct cytotoxicity. Another possible etiology involves similar stimulation of immune recognition of haptens. The last possible etiology suggests interaction directly between sulfonamide antibiotic and T-cells or antibodies without haptenation.

The first two etiologies suggest haptenation before stimulation of immune response. Evidence suggested that most of the non-type I hypersensitivity reactions of sulfonamide antibiotics were caused by metabolites.[25] It, therefore, makes the study of metabolites more interesting. One of the important metabolites is sulfamethoxazole hydroxylamine. Around 5% of sulfonamide absorbed will go through hydroxylation at N4 position by cytochrome P450 (CYP) 2C9. The sulfamethoxazole hydroxylamine is believed to cause both immunologic and non-immunologically mediated toxicities including thrombocytopenia, hepatitis, nephritis, lupus erythematosus and the classic sulfonamide hypersensitivity syndrome.[26-27]

Sulfamethoxazole hydroxylamine can be auto-oxidized intracellularly to a highly reactive nitroso-sulfonamide metabolite (Figure 6). Nitroso-sulfonamide can be acetylated and excreted

Besides direct cytotoxicity, nitroso-sulfonamides are also potent immunogens. It can bind covalently to T-cells or native proteins to induce type II, III or IV immune responses. These responses range from mild maculopapular rashes to life-threatening toxic epidermal necrolysis and Stevens-Johnson syndrome. The metabolic pathway of all these active metabolites starts from formation of sulfamethoxazole hydroxylamine by CYP2C9. And CYP2C9 is commonly expressed in skin, macrophages and liver. It was suggested that some skin rashes associated with sulfonamide antibiotics are due to formation of metabolite locally instead of systemically. Classic sulfonamide hypersensitivity syndrome is also known as a metabolite-mediated immune response.[25]

**Patient and disease specific hypersensitivity reactions**

Non-type I hypersensitivity response to sulfonamide is also believed to be patients and disease specific. Previous study isolated peripheral blood monocytes from patients with history of hypersensitivity and compared with patients without hypersensitivity. It found that their monocytes were more susceptible to damage by sulfonamide metabolites. Monocytes collected from parents of this group of patients also showed intermediate toxicity. It suggested predisposing pharmacogenetic defect though further information was needed to describe the relationship.[28] Another study also showed a possible link between HLA-B22 haplotype and susceptibility to sulfamethoxazole hypersensitivity.[29]

Incidence of sulfonamide antibiotic-associated hypersensitivity in AIDS patients is around 60% compared with 3% in general population. The reason for this observation is still unclear. One of the possible explanations is that the altered redox status of AIDS patients facilitates the transformation of sulfonamide hydroxylamines to nitroso-sulfonamides.[30]

**Parent compound or its metabolites?**

The above mentioned possible etiologies of non-type I hypersensitivity reaction stressed the importance of metabolites. Such etiology makes cross sensitivity between sulfonamide antibiotics and non-antibiotics impossible as they do not share the same metabolic pathways and yield the same kind of metabolites. Previous study supported the hypothesis that hypersensitive patients typically do not produce antibodies against the parent sulfonamide antibiotic.[31] It is, therefore, generally believed that un-metabolized non-haptenated drugs are immunologically benign.

This assumption was further affirmed by a recent study.[32] This study showed that 9.9% of patients, who were documented to have allergic reaction to a sulfonamide antibiotic, also experienced an allergic reaction to a sulfonamide non-antibiotic. On the contrary, only 1.6% of patients without history of sulfonamide antibiotic experienced hypersensitivity reaction to sulfonamide non-antibiotic. Higher percentage of concurrent sensitivity of both sulfonamide antibiotic and non-antibiotic apparently suggested cross sensitivity. However, this study showed even higher frequency (14%) of concurrent penicillin allergy in patients with history of sulfonamide antibiotic. The author finally concluded that allergic reactions to sulfonamide antibiotic and non-antibiotic are likely multiple, independent allergic reactions instead of cross sensitivity.

Case reports, however, showed contradictory results.[33-34] Two case reports showed cross sensitivity between trimethoprim-sulfamethoxazole with rofecoxib and nimesulide. Fixed drug eruptions were observed with similar appearance at identical location in both cases. As drug eruptions are often T-cell-mediated response, these two cases highly suggest a cross sensitivity between sulfonamide antibiotic and non-antibiotic in T-cell-mediated reaction. An in-vitro study indirectly suggested the possibility of cross sensitivity between sulfonamide antibiotic and non-antibiotic. It demonstrated T-cell proliferation in patients with history of allergic reaction to sulfonamide antibiotic when exposed to un-metabolized, non-haptenated sulfonamide.[35] It showed T-cell recognition of parent sulfonamide antibiotic in triggering allergic reaction. However, it cannot show whether T-cell recognizes the sulfonamide moiety or other parts of the molecule. Further study is definitely warranted in eluting the non-type I cross sensitivity reaction between sulfonamide antibiotic and non-antibiotic.

To summarize, IgE cross sensitivity reactions are largely unlikely between sulfonamide antibiotic and non-antibiotic as it is highly stereospecific and mediated by specific structure within the molecule (Table 1). Opinion about non-type I cross sensitivity is less consistent. Most evidence suggested low possibility of cross sensitivity as non-type I reactions are often preceded by metabolic transformation or haptenation. Direct T-cell responses are also observed in some cases and in-vitro study. Consensus therefore cannot be concluded in this circumstance.

**Table 1. Examples of drugs that belong to sulfonamide antibiotic and non-antibiotic**

| Sulfonamide antibiotic | | Sulfonamide non-antibiotic | |
|---|---|---|---|
| **Sulfonamide antibiotics** | | **Carbonic Anhydrase Inhibitors** | |
| Sulfamethoxazole | Sulfadiazine | Acetazolamide | Dorzolamide |
| Sulfacetamide | Sulfasalazine | **Sulfonylureas** | |
| **Sulfonamide antiretrovirals** | | Gliclazide | Glimepiride |
| Amprenavir | Fosampranavir | Glibenclamide | Gliperizide |
| | | **Loop Diuretics** | |
| | | Frusemide | Bumetanide |
| | | **Thiazide Diuretics** | |
| | | Hydrochlorothiazide | Indapamide |
| | | Chlorthalidone | Metolazone |
| | | Diazoxide | |
| | | **Anti-inflammatory** | |
| | | Celecoxib | |
| | | **Other *(sulfonamide moiety without benzene ring)*** | |
| | | Dapsone | Sumatriptan |
| | | Topiramate | Sotalol |
| | | Probenecid | |

**NSAID**

Non-steroidal anti-inflammatory drugs (NSAID) were reported to be the second most common cause of drug-induced hypersensitivity second to penicillin.[43] Clinical manifestations could be much diversified. They range from acute immediate type of allergic reactions to delayed type of reactions which can happen days or even weeks after drug exposure.

Within the group of NSAID, drugs of many different kinds of chemical structures are included. It is then impossible to explain the reaction with just one mechanism. Based on the cross-sensitivity pattern and manifestation with co-existing diseases, a few possible mechanisms of action have been suggested.

**Aspirin-Exacerbated Respiratory Disease (AERD)**

Also known as aspirin triad, asthma triad, Widal's syndrome, Samter's syndrome, aspirin-induced asthma, aspirin intolerant asthma or aspirin-sensitive rhinosinusitis / asthma syndrome,[44] AERD refers to the hypersensitivity reaction to aspirin and other NSAIDs in patients with upper airway (rhinosinusitis / nasal polyps) and lower airway (asthma) diseases. Until recently, it was stressed to be the underlying chronic inflammatory disease only occasionally exacerbated by aspirin or other NSAIDs.[45]

It was proposed that this is not an immunological reaction as cross-sensitivity reactions occur with NSAIDs of different chemical structures. Interestingly, NSAIDs with strong cyclooxygenase (COX) inhibition, like indomethacin, naproxen, diclofenac or ibuprofen tend to cause symptoms in a significant number of aspirin-hypersensitive patients (30-80%).[46] On the other hand, NSAIDs with weaker COX inhibition or higher selectivity to COX-2 seem to be better tolerated by patients with AERD.[47]

It is then reasonable to correlate AERD to COX inhibition. It has been proposed that inhibition of COX-1 (but not COX-2) would increase the local and systemic generation of cysteinyl leucotrienes and over-expression of cys$LT_1$ receptors as a result of the prostaglandin E2 deprivation.[48-49] Genetic polymorphisms and abnormal baseline arachidonic acid metabolism are also observed in this group of patients.[50-51] They often have increased levels of urinary leucotrienes and up-regulation of LTC4 synthase or cysteinyl LT receptors in the airway tissue.[50-51]

Clinically, it often happens in patients in around their 30's with a history of asthma and/or chronic rhinosinusitis complicated by recurrent nasal polyps.[52] Intake of various dose of aspirin (or NSAID) could trigger the reaction within 30 to 120 minutes. Aspirin doses ranging from 3mg to 600mg were reported to be able to trigger a reaction. At higher doses (100 – 600 mg), the incidence rate was lowered but the symptoms were often more severe and could be life-threatening. Common respiratory symptoms including rhinorrhea, nasal congestion, paranasal head pain, conjunctivitis, periorbital edema, laryngospasm, and asthma can occur upon the first exposure of a new NSAID. Extrapulmonary symptoms like flushing, transient hives, abdominal cramping pain, and less often, hypotension can also occur.[55]

As the risk of AERD cannot be easily predicted until the first ingestion of aspirin or NSAID, history of AERD and

avoidance of potential agents are essentially important in preventing future event. As previously mentioned, incidence of AERD is higher when patients with aspirin hypersensitivity were exposed to strong COX-1 inhibitors.[46] Strict avoidance of NSAIDs with moderate to strong COX-1 inhibitory activity is necessary. NSAIDs with weaker COX-1 inhibition can possibly be attempted with caution.

Paracetamol has relatively low COX-1 inhibitory activity. It could be a safe alternative for pain control. At low doses (below 500mg), the prevalence of adverse reaction ranges from 0–8.4% in NSAID- sensitive patients.[56] However, the prevalence of bronchial reactions increases up to 30% after ingestion of 1000mg paracetamol in NSAID-sensitive patients.[57] An oral tolerance test with a lower dose of paracetamol is therefore recommended.[51]

Preferential COX-2 inhibitors, e.g. Meloxicam and nimesulide, are quite well tolerated. About 86–96% of NSAID-sensitive patients can tolerate these agents at low dose.[58] Again, selectivity and tolerance are lost at higher doses. Hypersensitivity reactions can possibly be induced by preferential COX-2 inhibitors at higher dose.[59] Tolerance test should therefore be considered as well. Selective COX-2 inhibitors are generally well tolerated in AERD patients.[58] Desensitization may be necessary in some circumstances, e.g. coronary ischemic disease, when aspirin is left to be the best possible choice. Regular, daily ingestion of aspirin has to be maintained as tolerance disappears within 2-5 days after treatment interruption.[60] It was also observed that chronic treatment of aspirin after desensitization alleviates symptoms of rhinosinusitis and asthma and reduces systemic corticosteroid requirement.[61-62] It offers additional benefits in pharmacological treatment of AERD where treating the underlying chronic disease, which is equally important.

**NSAIDs-exacerbated urticaria/angioedema**

Ingestion of aspirin / NSAIDs in patients with chronic urticaria can exacerbate the underlying disease and induce hypersensitivity reaction with or without angioedema. Cross-sensitivity reaction is often seen in patients taking COX-1 inhibitors. It was therefore suggested that the mechanism of action is similar to that of AERD.[46] The theory was further supported by the observations of eicosanoids release in patients with skin eruption after ingestion of aspirin.[51, 63-64]

Urticaria can happen within 15 minutes of aspirin / NSAIDs ingestion or it can happen up to 24 hours after ingestion of the causative agent. The usual onset of symptoms is 1-4 hours.[51] Skin eruptions often take a few hours to resolve, but it may also persist for several days.[51] Symptoms can be fluctuating and it relates to the activity of the underlying chronic disease.[64]

As this type of hypersensitivity reaction is believed to be related to COX-1 inhibition, NSAIDs with COX-1 inhibition should be avoided. Paracetamol again was shown to be tolerated by 89.8% of patients.[65] However, selective COX-2 inhibitors may not be a solution to the problem. Tolerability to COX-2 inhibitors showed inconsistent results. One study showed good tolerability to rofecoxib, celecoxib and etoricoxib.[66] Another study showed celecoxib and rofecoxib induced skin reactions in 7-33% of patients upon controlled challenges.[67] Use of selective COX-2 inhibitors in this group of patients is still a controversy.

**Probable IgE-mediated reactions to aspirin and NSAIDs**

Some case reports of single-agent hypersensitivity reactions to aspirin and NSAIDs describe hypersensitivity symptoms which greatly resemble the symptoms the IgE-mediated reactions. Generalized urticaria, skin swelling and mucosal angioedema can be developed within minutes after ingestion of the causative agent. Symptoms progress to anaphylactic shock or even death. Anaphylactic shock was observed in 18-30% of patients hypersensitive to pyrazolones in the study.[68-69] However, the evidence showing the presence of IgE is limited.[51]

In patients with single-drug hypersensitivity reactions to pyrazolones, positive skin test and drug-specific serum IgE were found.[70] For other single-drug reactors, only anecdotal reports were able to detect specific IgE.[71] The most commonly found agents with this kind of reaction are pyrazolones, paracetamol, ibuprofen, diclofenac and naproxen.[68-69] As the evidence of the relationship between this kind of single-agent hypersensitivity reactions and IgE is unclear, it was suggested that the term *"Probable IgE-mediated reaction"* be used to describe this single-agent reaction and to differentiate it from COX-1 inhibiting reactions.

To prevent probable IgE-mediated reactions, strict avoidance of the causative agent and other chemically similar compounds is recommended. NSAIDs with different chemical structures can be attempted, but they should be used cautiously with tolerance test whenever possible.[51]

**Delayed reactions**

Symptoms which occur 24 hours after drug exposure are defined as delayed reactions although symptoms may develop in several days or weeks.[51] Limited data suggest that it could be a type IV reaction which is associated with drug-specific, cytotoxic T-cell reaction. However, systematic studies on this topic are lacking.[73-74]

**Summary**

As different mechanisms of action can be involved in the hypersensitivity reactions of NSAIDs, it is important to carefully study the natural history of symptoms and decide whether alternative agent is possible with the help of tolerance test when needed.

**ANTICONVULSANT**

Anticonvulsant Hypersensitivity Syndrome (AHS) is often associated with aromatic anticonvulsant drugs, e.g. phenytoin, carbamazepine and phenobarbital. It is a rare but serious adverse event. The incident rate is around 1 in every 1000 – 10,000 exposures. Clinical manifestations include a triad of symptoms including dermatologic rashes, fever and systemic organ involvement. It often leads to hospitalization or even death.[75] In this part, we will mainly discuss the rationale of cross-sensitivity, familial and genetic association, possible treatment and related co-morbidity.

**Clinical Manifestation**

Fever and rash happen in almost all of the patients with AHS.[75] The onset of symptoms varies; it ranges from 6 days to 12

weeks after the drug intake.[76-77] The type of rash of AHS may also vary. It could manifest as maculopapular rashes or as an exfoliative type like Steven-Johnson syndrome (SJS) or toxic epidermal necrolysis syndrome (TENS). As the clinical manifestations of both types of exfoliative rashes (SJS and TENS) are similar to AHS, and they often associate with drugs like aromatic anticonvulsants and sulphonamides, it is often hard to differentiate AHS with SJS and TENS. In that case, the possibility of AHS is easily ruled out.

Other systemic symptoms and signs, including lymphadenopathy, eosinophilia, lymphocytosis, leukocytosis, hepatitis, conjunctivitis or rarely myocarditis, could also be found in AHS. Reactivation of latent herpes viruses was also observed. Human herpes viruses including HHV-5 (cytomegalovirus), HHV-6 and HHV-7 were detected in some cases.[75] It is often detected 2-4 weeks after initial symptoms and it is often more severe.[75, 83]

**Mechanism of Action**

Although cross-sensitivity was observed between anticonvulsants with similar chemical structures, it was suggested that AHS was not an IgE-mediated reaction.[79] Instead, it was suggested that it was a type IV, T-cell mediated, delayed hypersensitivity reaction.[75] The exact mechanism of action was not fully elucidated, but it was considered to be related to deficiency or abnormality of the epoxide hydroxylase enzyme.

Aromatic anticonvulsants, like phenytoin, carbamazepine and phenobarbital (Figure 7A) are metabolized hepatically. After aromatic hydroxylation, arene oxides are formed (Figure 7B). Arene oxides are toxic reactive intermediates that are further metabolized to non-toxic metabolites. One of the important pathways involves microsomal epoxide hydroxylase (MEH). When there is a deficiency or abnormality of MEH, arene oxides cannot be metabolized. Accumulation of arene oxides can then cause cellular toxicity and cell death by covalently binding to macromolecules or by acting as antigens.[75, 80-82] Arene oxides are also considered to cause latent HHV reactivation by T-cell stimulation.[83]

**Cross-sensitivity**

A retrospective study found that 14 of 663 patients exposed to anticonvulsant drugs developed cross-sensitivity between two or more drugs, and it was primarily associated with exposure of phenytoin and carbamazepine.[84] In patients who initially developed a rash with carbamazepine, 10 of 25 patients developed a rash with phenytoin; whereas in patients who developed a rash with phenytoin, 10 of 17 patients developed rash to carbamazepine. For patients who developed a rash with phenobarbital at first, 4 out of 5 subsequently developed a rash with either carbamazepine or phenytoin. It was then concluded that the cross-sensitivity rate among aromatic anticonvulsants was around 40-80%.[75]

Newer anticonvulsants which also contain with an aromatic ring, e.g. lamotrigine and oxcarbazepine (Figure 8) should be considered for potential cross-sensitivity based on the assumption of arene oxides production. This assumption was further supported by the case reports of AHS associated with lamotrigine.[78, 85-86] In the previously mentioned study, patients with a history of AHS can safely tolerate benzodiazepine or valproic acid without adverse effect. Benzodiazepine, valproic acid and other non-aromatic anticonvulsants (Figure 9) were then considered to be the safe alternatives for patients with a history of AHS.

Familial association is another common concern of cross sensitivity among anticonvulsants, as anticonvulsants are often used for genetically related diseases like epilepsy. In vitro test showed a genetic link between patients with AHS and

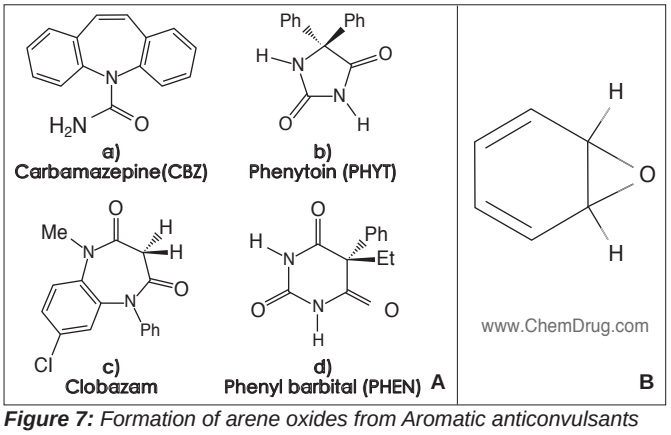


***Figure 7:*** *Formation of arene oxides from Aromatic anticonvulsants*

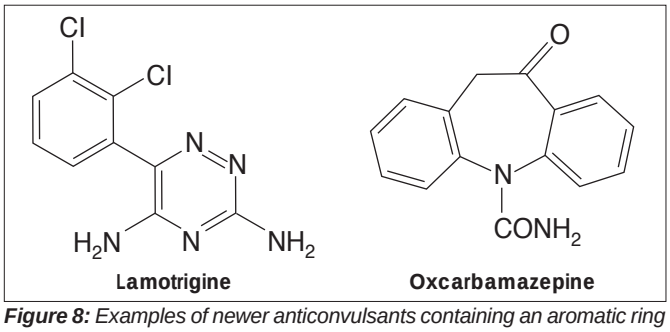


***Figure 8:*** *Examples of newer anticonvulsants containing an aromatic ring*

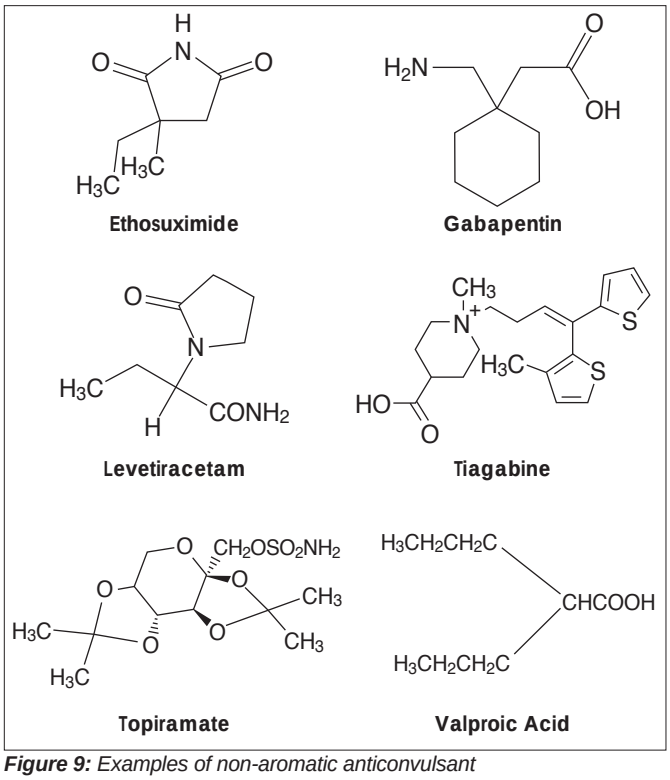


***Figure 9:*** *Examples of non-aromatic anticonvulsant*

their parents. The genetic link, however, was not consistently showed in the same study.[87] Another study which involved only one family showed more supporting results.[81] Five siblings of 3 patients with AHS were studied and 4 of them showed positive results in in-vitro cross-sensitivity test. Based on these results, familial association cannot be ruled out. It is then recommended to avoid aromatic anticonvulsants in family members of patients with a history of AHS.[75]

## Treatment

Identification of anticonvulsant hypersensitivity syndrome is very important, provided that there are quite a lot of other possible diagnoses in the context of similar clinical manifestations. Discontinuation of the causative agent is definitely the first thing to do. After that, systemic corticosteroid is often used. A wide range of doses of corticosteroid have been used.[75, 88-91] As a usual practice, steroid should be tapered down slowly; but in this case, not just because of steroid withdrawal, but also because of reoccurrence of AHS. In the previously mentioned case reports, AHS was worsened when steroids were discontinued prematurely.

Other treatment options have also been used, like antihistamines and intravenous immunoglobulin. However, data supporting their uses are limited. One study even showed increased mortality after treating SJS patients with intravenous immunoglobulin.[89, 92] Intravenous immunoglobulin was therefore recommended to be reserved for critically ill patients as a last resort.[75]

## Summary

Cross-sensitivity reactions with anticonvulsants are often associated with aromatic anticonvulsants. Avoidance of aromatic anticonvulsants is often necessary in patients with a history of Anticonvulsant Hypersensitivity Syndrome (AHS). Other considerations like family association and the treatment of delayed Human Herpes Virus (HVV) reactivation should also be born in mind.


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# Questions for Pharmacy Central Continuing Education Committee Program

*( Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)*

**2** CE Units

**Cross Sensitivity Reaction of Different Drug Classes**

1. ***Which one of the following drugs has the highest degree of chemical structure similarity with Penicillin?***
   A. Cephalexin (Ans)
   B. Cefuroxime
   C. Cefixime
   D. Ceftriaxone

2. ***What is the percentage of cross sensitivity reaction between Penicillin and Cephalosporin?***
   A. 0.5 – 6.5% (Ans)
   B. 6.5 – 9%
   C. 9 – 12%
   D. 40 – 80%

3. ***What is the percentage of cross sensitivity reaction between Penicillin and Carbapenem?***
   A. 0.5 – 6.5%
   B. 6.5 – 9%
   C. 9 – 12% (Ans)
   D. 40 – 80%

4. ***What is the definition of Sulfonamide?***
   A. Any compound containing sulphur
   B. Antibiotics derived from sulfanilamide
   C. Any compound with an $SO_2NH_2$ moiety (Ans)
   D. Any compound with an $SO_2NH_2$ moiety with a benzene ring.

5. ***Which of the following populations has the highest incidence of sulfonamide antibiotic-associated hypersensitivity reaction?***
   A. Paediatric population
   B. Geriatric population
   C. AIDS population (Ans)
   D. Post-transplant population

6. ***Which of the following patients has the highest risk of Aspirin hypersensitivity?***
   A. A 30 years old white woman with asthma (Ans)
   B. A 10 years old boy with eczema
   C. A 30 years old white man with eczema
   D. A 10 years old girl with eczema

7. ***Which one of the following statements is true?***
   A. NSAID cross sensitivity tends to be related to structure similarity
   B. Cross sensitivity between Aspirin and NSAID tends to be related to the degree of COX inhibition (Ans)
   C. NSAID hypersensitivity reaction tends to be related to T-cell reaction
   D. Patients with NSAID hypersensitivity tends to have normal baseline arachidonic acid metabolism

8. ***Which one of the following symptoms is NOT a common symptom of NSAID hypersensitivity?***
   A. Abdominal cramping pain
   B. Hypotension
   C. Chest pain (Ans)
   D. Paranasal head pain

9. ***What is the percentage of cross sensitivity among aromatic anticonvulsants?***
   A. 0.5 – 6.5%
   B. 6.5 – 9%
   C. 9 – 12%
   D. 40 – 80% (Ans)

10. ***What is the best first line treatment option for patients with Anticonvulsant Hypersensitivity Syndrome (AHS)?***
    A. Intravenous Antihistamine
    B. Intravenous Immunoglobulin
    C. Oral Corticosteroid (Ans)
    D. Topical Corticosteriod

***Answers will be released in the next issue of HKPJ.***

***CE Questions Answer for 202(D&T)***

**New approaches to HER2-positive breast cancer**

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

# No Improvement in Hand Skin Quality by Coenzyme Q10 Topical Formulation among Young and Old Healthy Female Volunteers

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**ABSTRACT**

**Objective:** This study aimed to evaluate the effectiveness of 0.085% coenzyme Q10 topical formulation (Q10-TF) in the improvement of hand skin quality among young and old healthy Chinese female volunteers. **Methods:** 102 healthy female undergraduates and 70 healthy female elderly were recruited in this double-blind, randomized and placebo-controlled trial. In Day 0, 14 & 28, subjects were assessed with transpidermal water loss (TEWL) measurement, and questionnaire with self-rated scores in hand skin's appearance, intactness, moisture, sensation, scaliness and wrinkles. After exclusion of subjects with hypersensitivity and non-compliance to interventions assigned, 71 female undergraduates and 68 female elderly were available for data analysis. **Results and Discussion:** Compared with placebo, Q10-TF offered no additional advantages in skin barrier function in terms of TEWL measurements, and all subjective evaluations of hand skin quality via questionnaire survey, over a period of 28 days. Vehicle-effect was pronounced among both younger and older subjects, particularly in self-rated scores in intactness, moisture, and wrinkles. **Conclusion:** A topical formulation containing coenzyme Q10 at the level of 0.085% was found to be ineffective in enhancing skin barrier function, in terms of TEWL values, and ineffective in improving subjective feelings in appearance, intactness, moisture, sensation, scaliness and wrinkles, compared with its control vehicle.

***Keywords:*** *Coenzyme Q10, Topical formulation, Skin quality, Clinical trial*

## INTRODUCTION

Coenzyme Q10 is used extensively in cosmetic products for a wide range of marketing claims due to its cutaneous anti-oxidizing and energizing properties. Since last century, it has already been shown to prevent photo-aging by effectively alleviating the UVA mediated oxidative stress present in human keratinocytes.[2] More current research in coenzyme Q10 anti-aging effects demonstrated that the mechanism of coenzyme Q10 involved may be related to epidermis protection against oxidative stress and enhancement of epidermal basement membrane components production.[6]

Low concentrations of topical coenzyme Q10, i.e., 0.01%, was found to stabilize isolated epidermal keratinocytes upon UV irradiation in healthy volunteers if applied twice daily for 7 days.[7] In a study investigating the inhibitory effect of coenzyme Q10 on UVB-induced wrinkle formation, twice daily application of 1% coenzyme Q10 cream for three months resulted in less wrinkle grade score.[3] Novel delivery methods of coenzyme Q10 have been reported, such as liposomal coenzyme Q10,[5] nanostructured lipid carriers[8] and solid lipid nanoparticles.[1]

Although there have been much advances in cosmetic efficacy of coenzyme Q10 in selected populations, such as those with photo-damaged skins, and new delivery strategies of the cosmetic active, there is still an important question remaining unanswered in literature: Can the beneficial effects observed for coenzyme Q10 in photo-damaged skin be translated to those with chronologically aged skin, or even to those young in ages? If coenzyme Q10 is useful for the chronologically-aged skin, or even for young skin, there should be improvement in both skin barrier function and subjective feeling of hand skin quality upon continuous applications. In this study, we aimed to address the question by conducting a double-blind, randomized and placebo-controlled trial among both young and old healthy female subjects for 28 days. Skin barrier function in terms of TEWL values would be evaluated, and self-rated scores in a validated hand skin evaluation questionnaire would be surveyed, allowing direct comparison between placebo and Q10-TF groups for both young and old healthy subjects.

## MATERIALS AND METHODS

### Formulations

The placebo and Q10-TF utilized in this study were manufactured by Macau Union Pharmaceutical Limited (Macao SAR, China) under GMP environment. Although there was minor color differences between the two preparations (Figure 1), subjects were unable to differentiate which one was actually coenzyme Q10 containing preparation. Master formula of the two preparations is summarized in Table 1. All chemical compositions, except coloring agent present in placebo and coenzyme 10 present in Q10-TF, are the same between the two preparations. Placebo was formulated as

a gel-based moisturizing preparation, as local consumers in Macao generally preferred the sensation of less greasy feeling for hand skin preparations. Coenzyme Q10 concentration at 0.085% was chosen because commercial cosmetic preparations in traditional formulations, i.e., gel, cream, lotion, usually contained coenzyme Q10 at the level of 0.01% - 0.2%. For instances, a cosmetic cream in market was found to contain 0.05% coenzyme Q10 upon HPLC analysis.[9]

***Figure 1:*** *Physical appearance of placebo (left) and Q10-TF (right).*

**Table 1. Master formula of placebo and 0.085% coenzyme Q10 topical formulations**

| Ingredient | Function | Placebo (%) | Q10-TF (%) |
|---|---|---|---|
| Carbopol 940 | Thickener | 0.50% | 0.50% |
| Triethanolamine | pH adjustment | 0.40% | 0.40% |
| Glycerin | Humectant | 10.00% | 10.00% |
| Methyl paraben | Preservative | 0.15% | 0.15% |
| Propyl paraben | Preservative | 0.05% | 0.05% |
| Propylene glycol | Humectant | 1.50% | 1.50% |
| Coenzyme Q10 | Active ingredient | -- | 0.085% |
| Coloring agent | Coloring agent | q.s. | -- |
| Purified water | Solvent | to 100% | to 100% |

HPLC analysis was performed to double-check the content of coenzyme Q10 in the two preparations. The protocol documented in Japanese Pharmacopoeia 15$^{th}$ edition was employed for HPLC analysis. Coenzyme Q10 eluted at retention time of 8.28 ± 0.05min (n=3). Excellent linearity ($R^2$ > 0.9999) was observed for the standard curve of peak area over coenzyme Q10 concentrations between 0.5mg/L and 200mg/L. It was confirmed that placebo and Q10-TF contained 0.000% ± 0.000% (n=3) and 0.085% ± 0.005% (n=3) coenzyme Q10 respectively, suitable for further clinical evaluations.

Subjects enrollment

102 healthy Chinese female undergraduates were recruited within School of Health Sciences, Macao Polytechnic Institute. The study period for the female undergraduates was from November, 2010 to December, 2010. 70 healthy Chinese female elderly were recruited in 4 elderly day care centers. The study period for the female elderly was from November, 2010 to February, 2011. The study period is within the seasons of late autumn to winter in Macao, where winter xerosis in hand skin is not uncommon among local populations, making it as the ideal timing for this cosmetic study.

Informed consents were obtained for all recruited subjects. The study has been approved by the research & ethics committees in both of School of Health Sciences, Macao Polytechnic Institute and the 4 elderly day care centers prior to subject enrollment. Subjects, who were pregnant, lactating, or hypersensitive to any ingredients in the two formulations, were excluded from the study. Subjects were randomly assigned to either placebo or Q10-TF group, according to the random number generated by a computer program during subject enrollment. All subjects were instructed to apply the assigned preparation with reasonable amounts three times daily for a consecutive 28 days, to maintain their normal daily activities, and to avoid application of other hand creams during the study period. Subjects could withdraw voluntarily at any times of the study. All subjects and assessors in cosmetic evaluations in this study were blinded from the knowledge of placebo and Q10-TF, and only the author knows the true identity of topical formulations during the whole course of study.

Cosmetic evaluations

In Day 0, 14 & 28, transepidermal water loss (TEWL) of subject's hand skin was assessed by Vapometer (Delfin Technologies Ltd, Finland). Subjects were not allowed to contact with water by their hands 1 hour before TEWL measurement. For the female undergraduates, all TEWL measurements were performed in standard laboratory conditions at 20 ± 1ºC and 40-60% relative humidity. For the female elderly, all TEWL measurements were performed in air-conditioned rooms at 20-25ºC inside the 4 elderly day care centers.

During each visit in Day 0, 14 & 28, every subject was required to fill a self-evaluation questionnaire on hand skin quality. The self-evaluation questionnaire was adopted from literature,[4] covering six 7-point Likert scale typed questions in hand skin's appearance, intactness, moisture, sensation, scaliness and wrinkles with 7-point being the highest quality and 1-point being the poorest quality in that category.

Data analysis

Data analysis was conducted by the author, who was not blinded during data evaluation. Subjects with fewer than 33% compliance, i.e., less than one application of topical preparation per day, were excluded from data analysis. Subject who missed the appointments in Day 14 and/or Day 28 were excluded for data analysis for those particular days, but their data available in other days were still retained for statistical analysis. Statistical analysis was then conducted to detect for the potential differences between pre- and post-tests, and between placebo and Q10-TF groups respectively.

## RESULTS AND DISCUSSION

Population demographics

One subject among young ladies, and one subject among old ladies, were found to be allergic to the topical preparation assigned and were excluded from the study.

30 female undergraduates had less than once application of their assigned topical preparation per day, and therefore, were excluded for any further data analysis because of their non-compliance. Population demographics and TEWL Day 0 values in female undergraduates are shown in Table 2a. No statistical differences in age and TEWL Day 0 values were observed between placebo and Q10-TF groups in female undergraduates. There were also no significant differences between dropout subjects and subjects available for data analysis among female undergraduates (data not shown). For old ladies, all of them had at least once application of their assigned topical preparation per day, and their compliance was in general much better than their younger counterparts. Population demographics and TEWL Day 0 values in female elderly are shown in Table 2b. No statistical differences in age and TWEL values were observed between placebo and Q10-TF groups in female elderly. The results indicated that the baseline skin water retention functions, prior to any topical treatments, were similar between placebo and Q10-TF groups among both young and old ladies in this study.

**Table 2a. Summary of TEWL data in Chinese female undergraduates**

| | Placebo | Q10-TF | p-value |
|---|---|---|---|
| Age | 19.2 ± 1.3 (n = 51) | 18.7 ± 1.0 (n = 51) | NS |
| TEWL values (g $m^{-2}$ $h^{-1}$) | | | |
| Day 0 | 17.60 ± 4.70 (n = 36) | 20.18 ± 6.91 (n = 35) | NS |
| Day 14 | 15.43 ± 11.54 (n = 33) | 15.11 ± 5.26 (n = 29) | NS |
| Day 28 | 21.25 ± 10.10 (n = 33) | 20.75 ± 3.82 (n = 32) | NS |
| Differences in TEWL values (g $m^{-2}$ $h^{-1}$) | | | |
| Day 14 – Day 0 | -2.21 ± 13.13 (n = 33) | -5.15 ± 9.37** (n = 29) | NS |
| Day 28 – Day 0 | +3.62 ± 12.14 (n = 33) | +0.38 ± 7.82 (n = 32) | NS |

Remark: * indicates the data in a particular group are statistically significant different between the two dates at $p < 0.05$
** indicates the data in a particular group are statistically significant different between the two dates at $p < 0.01$
NS indicates statistical non-significance at $p > 0.05$

**Table 2b. Summary of TEWL data in Chinese female elderly**

| | Placebo | Q10-TF | p-value |
|---|---|---|---|
| Age | 77.5 ± 7.8 (n = 36) | 78.6 ± 6.2 (n = 33) | NS |
| TEWL values (g $m^{-2}$ $h^{-1}$) | | | |
| Day 0 | 19.56 ± 13.00 (n = 36) | 19.85 ± 9.30 (n = 32) | NS |
| Day 14 | 17.35 ± 8.02 (n = 35) | 19.43 ± 11.36 (n = 30) | NS |
| Day 28 | 18.52 ± 10.30 (n =29) | 17.32 ± 12.66 (n = 27) | NS |
| Differences in TEWL values (g $m^{-2}$ $h^{-1}$) | | | |
| Day 14 – Day 0 | -2.09 ± 9.31 (n = 35) | -0.35 ± 8.47 (n = 30) | NS |
| Day 28 – Day 0 | -2.32 ± 9.17 (n = 29) | -3.04 ± 8.57* (n = 27) | NS |

Remark: * indicates the data in a particular group are statistically significant different between the two dates at $p < 0.05$
** indicates the data in a particular group are statistically significant different between the two dates at $p < 0.01$
NS indicates statistical non-significance at $p > 0.05$

Scores of 6 questions, i.e., appearance, intactness, moisture, sensation, scaliness and wrinkles, in self-evaluation questionnaire among female undergraduates and elderly are presented in Table 3a and Table 3b respectively. No statistical differences in any Day 0 scores were observed between placebo and Q10-TF groups in both populations. There were also no significant differences between dropout subjects and subjects available for data analysis among female undergraduates (data not shown). Both young and old subjects had high ratings on their skin appearance, intactness, scaliness and sensation, and moderate ratings on their skin moisture and wrinkles. While the results are understandable for the female elderly, the female undergraduates perceive their hand skin quality as not good enough. This could be due to the fact that the female undergraduates were indeed nursing, medical laboratory technician and pharmacy technician students, who were frequently exposed to hand disinfectant during their clinical internship. Hand damages among nurses were well-documented in literature.[4]

Effects of 0.085% coenzyme Q10 on hand skin quality

The differences of TEWL values between Day 14 and Day 0, and Day 28 and Day 0 among female undergraduates and elderly are summarized in Table 2a and 2b. No statistical significant differences were observed between placebo and Q10-TF groups in both populations. The score differences in self-evaluation questionnaire between Day 14 and Day 0, and Day 28 and Day 0 among female undergraduates and elderly are listed in Table 3a and 3b respectively. No statistical significant differences were again observed between placebo and Q10-TF groups in both populations. Overall speaking, the data indicated that the inclusion of 0.085% coenzyme Q10 in the topical formulation under investigation in this study did not offer any additional benefits in both skin barrier function, in terms of TEWL values, and self-rated scores in appearance, intactness, moisture, sensation, scaliness and wrinkles.

Vehicle-effects on hand skin among young and old ladies were evident in self-rated appearance, intactness, moisture, sensation, scaliness and wrinkles scores, and the effect was particularly pronounced in self-rated moisture scores (Tables 3a-3b). Although this study is a negative report in Q10-TF on TEWL measurements, and self-rated scores in appearance, intactness, moisture, sensation, scaliness and wrinkle, compared with placebo, it does suggest that coenzyme Q10 at 0.085% concentration in a conventional topical moisturizing formulation offers no additional benefits in skin barrier function and subjective improvement, and the observed benefits are solely due to vehicle-effect. It should be noted that in commercial cosmetic hand cream preparations, it is not uncommon for coenzyme Q10 to be present at concentrations lower than 0.085%, and therefore, their claimed efficacy is highly questionable.

## CONCLUSION

Compared with the control vehicle, 0.085% coenzyme Q10 topical formulation offers no additional benefits in terms of skin

barrier function analyzed by TEWL measurements, and self-rated scores in appearance, intactness, moisture, sensation, and wrinkles, among young and old healthy Chinese ladies. Large vehicle-effects are observed in all subjective evaluations, particularly in intactness, moisture and wrinkles, in both young and old subjects in this study.

**Table 3a. Summary of self-evaluation data in Chinese female undergraduates**

| | Placebo (n=34) Median (IQR) | Q10-TF (n=33) Median (IQR) | p-value between placebo & Q10-TF |
|---|---|---|---|
| Appearance: | | | |
| Day 0 | 7.00 (1.00) | 6.00 (1.00) | 0.712 |
| Day 14 – Day 0 | 0.00 (1.00)* | 0.00 (1.00)* | 0.825 |
| Day 28 – Day 0 | 0.00 (1.00) | 0.00 (1.00) | 0.527 |
| Intactness | | | |
| Day 0 | 6.00 (2.00) | 5.00 (2.00) | 0.181 |
| Day 14 – Day 0 | 0.00 (1.00)* | 1.00 (2.00)** | 0.088 |
| Day 28 – Day 0 | 0.00 (1.00) | 1.00 (1.00)** | 0.321 |
| Moisture | | | |
| Day 0 | 4.00 (2.00) | 5.00 (1.00) | 0.208 |
| Day 14 – Day 0 | 1.00 (2.00)** | 1.00 (2.00)* | 0.253 |
| Day 28 – Day 0 | 1.00 (2.00)** | 1.00 (3.00)* | 0.333 |
| Sensation | | | |
| Day 0 | 7.00 (1.00) | 6.00 (1.00) | 0.373 |
| Day 14 – Day 0 | 0.00 (1.00) | 0.00 (1.00) | 0.852 |
| Day 28 – Day 0 | 0.00 (1.00) | 0.00 (1.00) | 0.727 |
| Scaliness | | | |
| Day 0 | 6.00 (2.00) | 6.00 (1.00) | 0.952 |
| Day 14 – Day 0 | 1.00 (2.00)** | 1.00 (1.00)** | 0.994 |
| Day 28 – Day 0 | 0.00 (1.00)* | 1.00 (1.00)* | 0.802 |
| Wrinkles | | | |
| Day 0 | 4.00 (2.00) | 5.00 (3.00) | 0.266 |
| Day 14 – Day 0 | 0.50 (1.00)** | 0.00 (2.00) | 0.039 |
| Day 28 – Day 0 | 1.00 (2.00)** | 0.00 (1.75)* | 0.271 |

Remark: * indicates the data in a particular group are statistically significant different between the two dates by Wilcoxon signed ranks tests at $p < 0.05$
** indicates the data in a particular group are statistically significant different between the two dates Wilcoxon signed ranks tests at $p < 0.01$

**Table 3b: Summary of self-evaluation data in Chinese female elderly**

| | Placebo (n=36) Median (IQR) | Q10-TF (n=32) Median (IQR) | p-value between placebo & Q10-TF |
|---|---|---|---|
| Appearance: | | | |
| Day 0 | 7.00 (0.00) | 7.00 (0.00) | 0.789 |
| Day 14 – Day 0 | 0.00 (0.00) | 0.00 (0.00) | 0.548 |
| Day 28 – Day 0 | 0.00 (0.00) | 0.00 (0.00) | 0.732 |
| Intactness | | | |
| Day 0 | 7.00 (1.00) | 7.00 (2.00) | 0.439 |
| Day 14 – Day 0 | 0.00 (1.00)* | 0.50 (1.25)** | 0.240 |
| Day 28 – Day 0 | 0.00 (1.50) | 0.00 (1.00)* | 0.761 |
| Moisture | | | |
| Day 0 | 4.00 (3.00) | 3.00 (2.75) | 0.301 |
| Day 14 – Day 0 | 2.00 (4.00)** | 2.00 (2.00)** | 0.424 |
| Day 28 – Day 0 | 2.00 (3.50)** | 2.00 (4.00)** | 0.431 |
| Sensation | | | |
| Day 0 | 7.00 (1.00) | 7.00 (1.00) | 0.874 |
| Day 14 – Day 0 | 0.00 (1.00) | 0.00 (0.00)* | 0.929 |
| Day 28 – Day 0 | 0.00 (1.00)** | 0.00 (0.00)* | 0.484 |
| Scaliness | | | |
| Day 0 | 7.00 (0.00) | 7.00 (1.00) | 0.104 |
| Day 14 – Day 0 | 0.00 (0.00) | 0.00 (1.00)* | 0.134 |
| Day 28 – Day 0 | 0.00 (0.00) | 0.00 (0.00) | 0.410 |
| Wrinkles | | | |
| Day 0 | 4.00 (2.00) | 3.00 (3.00) | 0.166 |
| Day 14 – Day 0 | 0.00 (3.00) | 0.00 (4.00) | 0.936 |
| Day 28 – Day 0 | 1.00 (3.00) | 0.00 (3.00)* | 0.617 |

Remark: * indicates the data in a particular group are statistically significant different between the two dates by Wilcoxon signed ranks tests at $p < 0.05$
** indicates the data in a particular group are statistically significant different between the two dates Wilcoxon signed ranks tests at $p < 0.01$


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## DISCLOSURE

The author receives no financial rewards from Macau Union Pharmaceutical Limited (Macao SAR, China).


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# "Chinese Medicines are Toxic" is a Misconception

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**ABSTRACT**

**Recent widespread rumors that "Chinese Medicines are toxic" are misunderstood. As experts commented whether a substance is toxic or not, very often depends on its physicochemical form, part, method of processing, and period of consumption. Depending on how and when it is used, the effect of Chinese Medicines (CM) could also be significantly different. Various results have been described and it is misleading to be uniformly saying that they are toxic. In Europe and the United States, most CM are regulated under food standards and safety. This reflects that the majority of CM are safe as long as they are properly prescribed and used. Since the philosophical approach between Western and Chinese medical practice is different, consumers have frequently been misled by the media on the effects of CM. The worse aspect of CM is their improper use by people as far as the safety issue of CM is concerned.**

***Keywords:*** *Chinese medicines (CM), Western drugs, Toxicity, Safety, Heavy metals, Cinnabar, Betel Nut, Ranunculaceae aconitum, aristolochic acid*

## INTRODUCTION

Chinese medicines (CM) are the traditional treasures of China. Their uses in medical treatment and health improvement have been introduced over several millennia. Nevertheless, it is an old topic that CM contains excessive levels of heavy metals and other toxicants. Hence, people regard them as toxic and should not be used. In this article, we would like to address and explore a few incidences which lead to the public getting the conception that CM are unsafe for consumption.

## REPORTED CASES OF UNSAFE USES OF CM

Recently, there has been widespread concern about excessive levels of heavy metals in CM. In fact, this is an old topic in the field.[1-3] Amongst these so-called "excessive" events, one of the most typical features is reported by the media that overseas markets found excessive toxic CM, which caused uproar within the country. For instance, the Department of Health in Hong Kong announced that there are certain amounts of "Jiantiwubuwan" (Fig. 1A) pills manufactured by Tongrentang (TRT) which were found to contain an excessive level of mercury.[4] In other reported cases, two products, namely "NiuHuangqianjinsan" (Fig. 1B) and "Xiaoerzhibaowan" pills (Fig. 1C) were found with excessive levels of cinnabar.[5]


***Figure 1:*** *Some Chinese proprietary medicinal products containing high level of cinnabar. A = Jiantiwubwan ; B = NiuHuangqianjinsan; C = Xiaoerzhibaowan.*

Although both cinnabar and mercury are "Gong" (mercury) in Chinese, they represent two different forms of the same thing.[6] Professor Qian Zhongzhi, the chief consultant of the Chinese Pharmacopoeia Commission, commented that the toxicity of mercury on the human body mainly depends on its physicochemical form. The main form of cinnabar is mercury sulfide (HgS), which is a typical covalent compound, chemically stable, less or almost insoluble in hydrochloric acid and nitric acid. It is difficult to decompose in the stomach and absorbed by the body. Therefore, evaluation of the amount of cinnabar and proprietary Chinese medicines (pCM) containing cinnabar cannot simply be applied to determine the toxicity of "Gong". Instead people should be educated to distinguish the physicochemical forms and the valence state of these two forms of "Gong". Hence, the toxicity of Gong in cinnabar is incomparable to the other form even though they are derived from the sane chemical element.[7] Professor Xu Rongqian, who is a Pediatrics doctor in Beijing Dongzhimen Hospital, commented that cinnabar is frequently used clinically in risky, acute, severe illnesses. He personally has never come

across a case of poisoning or adverse reactions due to the treatment with cinnabar or proprietary Chinese medicine containing cinnabar ingredients in children. Indeed, cinnabar is present in many famous traditional Chinese medicines for first aid, e.g. "3 Treasures": "Angongniuhuangwan" (Fig. 2A), "Quofangbaoyuen" (Fig. 2B) and "Zixue Dan" (Fig. 2C). When Miss LIU Hairuo, who was a Phoenix TV reporter, was declared brain dead due to a car accident in the UK, she recovered from this fatal damage and could even speak and walk after switching to TCM treatment in China. In the course of the treatment process, "Angongniuhuangwan" was used. Hence, it demonstrates that what looks toxic can actually heal a patient.[8]

Prior to this event, another Chinese medicine "Zhengtian Wan" (Figure 2D), produced by China Resources Sanjiu Group that has been used for the treatment of headache, was claimed toxic to the heart and nervous system in the UK media because it contains Aconitum grass, which was regarded by ancient Greeks as "the queen of poison" herbs. However, an official response from Sanjiu Group denied that the Aconite added into "Zhengtian Wan" pills was a processed not the native aconite. It is true that this herb, which is the sub-root of *Ranunculaceae aconitum*, possesses highly toxic substance in its native form. However, after heat processing the monkshood Aconitum, whose toxicity due to the presence of aconite alkaloids, is significantly reduced.[9,10]

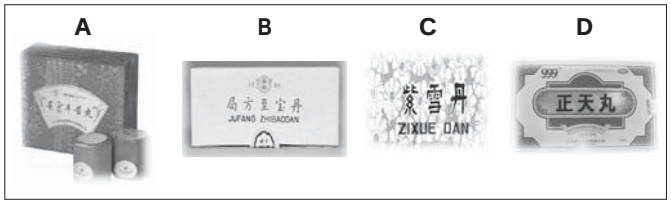


***Figure 2:*** *Chinese proprietary medicinal products containing some toxic botanical materials in their native form. Product A = Angongniuhuangwan; B = Quofangbaoyuen; C = Zixue Dan and D = Zhengtian Wan.*

## "CHEWING BETEL NUT" AND "BETEL NUT MEDICINE"

In another case, "Simontang", which is Hansen Pharm's first launched pharmaceutical product, was accused of containing carcinogens of betel nut.[11,12] The accusation in 2003 stemmed from an article that listed betel nut, tobacco and another 118 kinds of substances under the category of carcinogens. Subsequently, many articles written by journalists in Southeast Asia, such as Malaysia, Thailand and India jumped to the conclusion that prolonged chewing of betel nut will promote a higher incidence of oral cancer based on an epidemiological survey.[13,14]

Truly continuous chewing of the betel nut may lead to the development of oral cancer but taking the betel nut as a medicine is a fundamentally different issue.[15] In response to these reports, Li Lianda from the Chinese Academy of Engineering summed up by listing a few "differences". Firstly, he commented that the raw material used for medication is not the same part of the herb. Betel nuts used for chewing are the young fruit and those for medication purposes are mature medicinal betel nuts. Secondly, the nuts collected at two different stages are not processed by the same method. In brief, "chewing betel nut" is soaked with lime, an alkaline substance which can easily cause irritation to oral mucosa. Chinese betel nut for medication purposes, however, is subjected to a series of processes including cleaning, extraction and decoction. Throughout the whole process, obvious detoxification takes place. Thirdly, there is no similarity as far as the entrance site is concerned. For chewing betel nut, some people chew for a few hours, while the Chinese betel nut is orally taken in a decoction form, not long enough to stimulate the oral mucosa. Fourthly, the amount of consumption is not the same. There is no limit for chewing the betel nut; which means a substantially high amount of carcinogens might be absorbed while for medical purposes, generally 3-5 grams of betel nut per day are prescribed.

## DIFFERENCES BETWEEN THE PHILOSOPHY OF THE WESTERN AND THE CHINESE MEDICINES

Fang Shuting, who is the Chairman of the Chinese Medicine Association in China, commented that the misconception is attributed to misunderstanding of CM by some overseas consumers.[16] Since the philosophical practice of Western medicine is different from that of Chinese medicine, it is quite likely that medicines are harmful if people view them as substance to combat other molecules in our body. However, if they are treated as part of an organic body, they can serve as a health promoting substance.[17]

## IMPROPER USE OF CM COULD BE HARMFUL TO HEALTH

The key issue of the clinical safety of CM is not its' toxicity but whether it is medicated properly. Improper use of CM is indeed the worse scenario. The "Longdanxieganwan incident", which happened from 1990's to the early years of this century, is a typical example. The incident stemmed from peoples' ignorance of the practice of Chinese medicine. As they did not practice according to the differentiation theory of TCM, patients were prescribed with long-term use of traditional Chinese medicines containing aristolochic acid, which resulted in kidney failure in the patients.[18] Consequently, some people made use of this incident to hype the media, and ultimately as many as 70 kinds of Chinese herbal medicines were implicated, causing an "aristolochic acid event."[19-22]

Liang Aihua is a researcher in the China Academy of Chinese Medical Sciences. She pointed out that practice of Chinese medicines in China follows the compliance and syndrome differentiation theory of TCM, which causes no serious problems. While there is no proper coaching abroad during the practice problem arise is inevitable. But even a few problems arise in foreign countries should not put the use of CM under a ban or generate any ill feelings. Western medicine has its side effects too, yet they are not banned. The key solution is rational use of the drug.

There an ancient saying the evil of drugs is medicated not properly. Leaving the overall concept of TCM, diagnosis and treatment, and not understanding the differentiation of symptoms and monarch, disorderly use or abuse of TCM, it is easy to go wrong. As Xu Lingtai, a famous doctor in the Qing Dynasty said, herbal substances like licorice and ginseng could become poisons if they are improperly used. Wang Chengde, who is a CPPCC member, commented whether

medicine is toxic or non-toxic depends on whether it is certified to use. As long as it is properly used in the right way, toxic substances are also safe. Contrary, incorrect treatment, even nontoxic herbs could be poisonous. He suggested that people should be educated with correct understanding of the toxicity of traditional Chinese medicine.[23]

Another old saying hints that one should not take a doctor's medicine if he has insufficient experiences of treatment. This means if medical doctors do not have solid medical knowledge, avoid taking their drugs. It was pointed out by Liu Changhua, who is a researcher from the China Academy of Traditional Chinese, that the major reason cinnabar mercury might induce toxic effect is the improper use of the substance as a health product for excessive and prolonged periods of time instead of a short term medication as a drug. Chinese medication always pays attention to "the disease lasts", as long as under the guidance of a doctor. In accordance with the safe dosage, taking medication should not lead to health problems.

A Beijing Traditional Chinese Medicine Bureau officer referred to documents in "Shen Nong's Herbal Classic" and commented that heavy metals and other minerals, such as cinnabar, native copper and gypsum have indeed been used as therapeutic substances in traditional Chinese medicines. These minerals have more than several thousand years of clinical practices. Many veterans reported that they provide better clinical effects over other drugs. Their efficacy is better than some generic drugs as they do not give significant effects. Hence, heavy metals added into CMs have their advantages and they should be treated as an integral part in the Chinese medicines. In fact, the safety issue of medicines at the clinical stage lies not in its toxicity, but rather whether they are properly used. Many toxic drugs can give therapeutic effects at clinical stage as long as they are properly used based on proper monitor of compound compatibility and accurate diagnosis.[24]

Toxicity does not exist only in traditional Chinese medicines and Chinese medicines, indeed, many damaging effects on the human body are also observed in many western medicines; for instances, development of deaf is always associated with the usage of streptomycin, and it is a risky treatment whenever applying gentamycin as it causes damage in kidney after prolong use. However, the toxic effects of these drugs do not constitute a full stop of their uses by doctors as long as they are properly monitored according to Liang Aihua's opinion.

Another medical expert, Qian Zhongzhi commented that about 30% of drugs sold in market and used today have some toxicity and side effects. No one can guaranteed a 100% safe of their use. Hence, it is impossible to find a drug free from any risks. By following the doctor's medication guide to patient and his experiences, we can effectively avoid drugs risks.

## WRONG APPROACH TO EVALUATING THE SAFETY OF CM

TCM is not recognized as medicine in Europe and in the United States. Hence, food standards are used as the basis for assessing TCM no matter it is sold in domestic or exported oversea. Many countries and regions, including Hong Kong, Southeast Asian countries and Japan, mandate heavy metal limits for TCM, as is used in food standards.[25]

Drugs consisting of heavy metals cannot simply be assessed with the standard for food but only for reference because drugs are not the same as food. They are not consumed largely and frequently. They should be taken under the guidance of a doctor temporarily under limited usage. Wang Chengde commented that if food standard were adopted for CM, it will limit its use. In particular, for traditional Chinese medicines containing high amount of heavy metals, it would be concluded that they should not be used as they are toxic. Consequently, many distinctive Chinese medicine treatment methods would be banned or lost and therapeutic efficacy of some CM would be greatly reduced.[26,27]

## CONCLUSION

The so-called Chinese "exceeded" event is actually caused by different standards, different measurement methods, which make the different valuation results. When cinnabar made medicine, the determination of which toxic soluble mercury free, the current international approach are destroyed digestion method, the result is that in the destruction and elimination of the organic disturbance, while insoluble cinnabar (HgS) into the toxic $Hg^{2+}$, $Hg^{+}$. Since the testing of material and people taking the subsitance is not the same kind of form' it will come to result that CM mercury exceeded ten and hundreds of times.

Li Lianda worried that the development of TCM industry would be hampered if CM are banned once any components in CM found toxic according to the criteria of food standards. Liang Aihua also commented that it is irrational to come to conclusion that a CM is unsuitable for use based merely on the toxicity of a single component without considering other characteristics and processing. Liu Changhua mentioned that CM stress on the nature treatment, while Western medicine based on ingredients. There are significant differences between Chinese and Western medicine, Chinese medicine with western medicine criteria to evaluate it is a lack of respect for traditional Chinese medicine. Mercury is used in chemical atomic absorption method, is detected by all the mercury components cinnabar, and not only free mercury. Therefore, in order to accuse toxic medicine is unreasonable.

It is an important issue for the development of TCM industry to promote quality evaluation system research in the field. Qian Zhongzhi mentioned that it is a new job to regulate the levels and limits of heavy metal in TCM. It is eventually expected to form a scientific standard under the conditions of safety considering the availability of resources and other factors continue to accumulate data and experiences. Qian Zhongzhi agreed that it is an important and urgent matter to develop a method for testing different forms of mercury whether it is the valence or the element form of Hg. The method will benefit the quality control of CM containing cinnabar. This task has been commissioned by the Chinese Pharmacopoeia Commission to Shanghai Institute for Drug Control. A new method is expected to be available and officially listed in the 2015 edition of the Chinese Pharmacopoeia.[28,29]

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CUHK DH HA HKU PSHK PPA SHPHK

## AFINITOR®
(Novartis Oncology)

**Active Ingredient:**
Everolimus

**Presentation:**
Each tablet containing10 mg of everolimus and 297 mg lactose; each tablet contains 5 mg of everolimus and 149 mg lactose

**Pharmacological Properties:**
Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, protein kinase inhibitors, ATC code: L01XE10 . Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor. mTOR is a key serine-threonine kinase, the activity of which is known to be upregulated in a number of human cancers. Everolimus binds to the intracellular protein FKBP-12, forming a complex that inhibits mTOR complex-1 (mTORC1) activity. Inhibition of the mTORC1 signaling pathway interferes with the translation and synthesis of proteins by reducing the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4EBP-1) that regulate proteins involved in the cell cycle, angiogenesis and glycolysis. S6K1is thought to phosphorylate the activation function domain 1 of the oestrogen receptor, which is responsible for ligand-independent receptor activation. Everolimus reduces levels of vascular endothelial growth factor (VEGF), which potentiates tumour angiogenic processes. Everolimus is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood-vessel-associated smooth muscle cells and has been shown to reduce glycolysis in solid tumours in vitro and in vivo.

**Indications:**
Hormone receptor-positive advanced breast cancer
Afinitor is indicated for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.
Neuroendocrine tumours of pancreatic origin
Afinitor is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.
Renal cell carcinoma
Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

**Dosage and Administration:**
The recommended dose is 10 mg everolimus once daily. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. If a dose is missed, the patient should not take an additional dose, but take the usual prescribed next dose.
Dose adjustment due to adverse reactions
Management of severe and/or intolerable suspected adverse reactions may require dose alterations. Afinitor may be dose reduced or temporarily withheld (e.g. for one week) followed by reintroduction at 5 mg daily. If dose reduction is required, the suggested dose is 5 mg daily).
Paediatric population
The safety and efficacy of Afinitor in children aged 0 to 18 years have not been established. No data are available.
Elderly patients (≥65 years)
No dose adjustment is required.
Renal impairment
No dose adjustment is required.

Hepatic impairment
For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily. Everolimus has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) and is not recommended for use in this patient population.

Method of administration
Afinitor should be administered orally once daily at the same time every day, consistently either with or without food. Afinitor tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.

**Contraindications:**
Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients.

**Warnings:**
Non-infectious pneumonitis
Non-infectious pneumonitis is a class effect of rapamycin derivatives, including Afinitor. Non-infectious pneumonitis (including interstitial lung disease) was described in 12% of patients taking Afinitor. Some cases were severe and on rare occasions, a fatal outcome was observed. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Afinitor therapy without dose adjustments If symptoms are moderate, consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Afinitor may be re-initiated at 5 mg daily.

For cases where symptoms of non-infectious pneumonitis are severe, Afinitor therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with Afinitor may be re-initiated at 5 mg daily depending on the individual clinical circumstances.

Infections

Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens. Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis or candidiasis, and viral infections including reactivation of hepatitis B virus, have been described in patients taking Afinitor. Some of these infections have been severe (e.g. leading to respiratory or hepatic failure) and occasionally fatal.

Physicians and patients should be aware of the increased risk of infection with Afinitor. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with Afinitor. While taking Afinitor, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Afinitor.

If a diagnosis of invasive systemic fungal infection is made, Afinitor treatment should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy.

Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus.

Oral ulceration

Mouth ulcers, stomatitis and oral mucositis have been observed in patients treated with Afinitor. In such cases topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed.

**Pregnancy and lactation:**

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must use a highly effective method of contraception (e.g. oral, injected, or implanted non-oestrogen-containing hormonal method of birth control, progesterone-based contraceptives, hysterectomy, tubal ligation, complete abstinence, barrier methods, intrauterine device [IUD], and/or female/male sterilisation) while receiving everolimus, and for up to 8 weeks after ending treatment.

Pregnancy

There are no adequate data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects including embryotoxicity and foetotoxicity. The potential risk for humans is unknown.

Everolimus is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether everolimus is excreted in breast milk. However, in rats, everolimus and/or its metabolites readily pass into the milk. Therefore, women taking everolimus should not breast-feed.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be advised to be cautious when driving or using machines if they experience fatigue during treatment with Afinitor.

**Side effects:**

a) Summary of safety profile

Three randomised, double-blind, placebo controlled phase III studies contribute to the safety profile. The respective exposure in the phase III studies was:

- BOLERO-2 (CRAD001Y2301): everolimus in combination with exemestane in the treatment of postmenopausal women with oestrogen receptor-positive, locally advanced or metastatic breast cancer who were previously treated with either letrozole or anastrozole. In total, 191 (40%) patients were exposed to everolimus therapy for ≥32 weeks. The rates of adverse reactions resulting in permanent discontinuation were 21% and 3% for the everolimus plus exemestane and the placebo plus exemestane treatment groups, respectively.
- RADIANT-3 (CRAD001C2324): everolimus plus best supportive care in patients with advanced neuroendocrine tumours of pancreatic origin. In total, 63 (31%) patients were exposed to everolimus 10 mg/day for ≥52 weeks. The rates of adverse reactions resulting in permanent discontinuation were 14% and 2% for the everolimus and placebo treatment groups, respectively.
- RECORD-1 (CRAD001C2240): everolimus plus best supportive care in patients with metastatic renal cell carcinoma. In total, 165 patients were exposed to everolimus 10 mg/day for ≥4 months. The rates of adverse reactions resulting in permanent discontinuation were 7% and 0% for the everolimus and placebo treatment groups, respectively. Most adverse reactions were grade 1 or 2 in severity.

The most frequent grade 3-4 adverse reactions (incidence ≥2% in at least one phase III study) were anaemia, fatigue, diarrhoea, infections, stomatitis, hyperglycaemia, thrombocytopenia, lymphopenia, neutropenia, hypophosphataemia, hypercholesterolaemia, diabetes mellitus, and pneumonitis. The grades follow CTCAE Version 3.0.

b) Tabulated summary of adverse reactions

Table 2 shows the incidence of adverse reactions reported for patients receiving everolimus 10 mg/day in at least one of the pivotal studies. All terms included are based on the highest frequency reported in a pivotal study. Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| Table 2 Adverse reactions | |
|---|---|
| Infections and infestations | |
| Very common | Infections[a, *] |
| Blood and lymphatic system disorders | |
| Very common | Anaemia, thrombocytopenia |
| Common | Leukopenia, lymphopenia, neutropenia |
| Uncommon | Pure red cell aplasia |
| Immune system disorders | |
| Not known | Hypersensitivity |
| Metabolism and nutrition disorders | |
| Very common | Hyperglycaemia, hypercholesterolaemia, hypertriglyceridaemia, anorexia |
| Common | Diabetes mellitus, hypophosphataemia, hypokalaemia, hyperlipidaemia, hypocalcaemia, dehydration |
| Psychiatric disorders | |
| Common | Insomnia |
| Nervous system disorders | |
| Very common | Dysgeusia, headache |
| Uncommon | Ageusia |
| Eye disorders | |
| Common | Conjunctivitis, eyelid oedema |
| Cardiac disorders | |
| Uncommon | Congestive cardiac failure |
| Vascular disorders | |
| Common | Hypertension, haemorrhage[b] |
| Uncommon | Flushing, deep vein thrombosis |
| Respiratory, thoracic and mediastinal disorders | |
| Very common | Pneumonitis[c], dyspnoea, epistaxis, cough |
| Common | Pulmonary embolism, haemoptysis |
| Uncommon | Acute respiratory distress syndrome |
| Gastrointestinal disorders | |
| Very common | Stomatitis[d], diarrhoea, mucosal inflammation, vomiting, nausea |
| Common | Dry mouth, abdominal pain, oral pain, dysphagia, dyspepsia |
| Hepatobiliary disorders | |
| Common | Alanine aminotransferase increased, aspartate aminotransferase increased |
| Skin and subcutaneous tissue disorders | |
| Very common | Rash, dry skin, pruritus, nail disorder |
| Common | Palmar-plantar erythrodysaesthesia syndrome, erythema, skin exfoliation, acneiform dermatitis, onychoclasis, skin lesion, mild alopecia |
| Uncommon | Angioedema |
| Musculoskeletal and connective tissue disorders | |
| Common | Arthralgia |
| Renal and urinary disorders | |
| Common | Creatinine increased, renal failure (including acute renal failure)*, proteinuria* |
| General disorders and administration site conditions | |
| Very common | Fatigue, asthenia, peripheral oedema, pyrexia |
| Common | Chest pain |
| Uncommon | Impaired wound healing |
| Investigations | |
| Very common | Weight decreased |

* see also Description of selected adverse reactions"

[a] Includes all reactions within the 'infections and infestations' system organ class (such as pneumonia, sepsis, and isolated cases of opportunistic infections [e.g. aspergillosis, candidiasis and hepatitis B )

[b] Includes different bleeding events not listed individually

[c] Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar haemorrhage, pulmonary toxicity, and alveolitis

[d] Includes stomatitis and aphthous stomatitis, and mouth and tongue ulceration

**Forensic Classification**
P1S1S3

## Edarbi ® Tablets
**(Takeda Pharmaceutical)**

*Prepared by Anthony Fan and edited by Lucillia Leung*

**Active Ingredient:**
Azilsartan Medoxomil

**Presentation:**
Each tablet contains 40 mg or 80 mg azilsartan medoxomil in the pack of 28's.

**Pharmacological Properties:**
Azilsartan medoxomil is an orally active prodrug that is rapidly converted to the active moiety, azilsartan, which selectively antagonises the effects of angiotensin II by blocking its binding to the AT1 receptor in multiple tissues. Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium.

Blockade of the AT1 receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increases in plasma renin activity and angiotensin II circulating levels do not overcome the antihypertensive effect of azilsartan.

**Indications:**
Edarbi is indicated for the treatment of essential hypertension in adults.

**Dosage and Administration:**
The recommended starting dose is 40 mg once daily, with or without food. The dose may be increased to a maximum of 80 mg once daily for patients whose blood pressure is not adequately controlled at the lower dose. Near-maximal antihypertensive effect is evident at 2 weeks, with maximal effects attained by 4 weeks.

No initial dose adjustment with Edarbi is necessary in elderly patients (65 years and over), although consideration can be given to 20 mg as a starting dose in the very elderly (≥ 75 years), who may be at risk of hypotension.

The safety and efficacy of Edarbi in children and adolescents 0 to < 18 years have not yet been established.

For hypertensive patients with severe renal impairment and end stage renal disease, caution should be exercised, as there is no experience of use of Edarbi in these patients. Hemodialysis does not remove azilsartan from the systemic circulation. No dose adjustment is required in patients with mild or moderate renal impairment.

Edarbi has not been studied in patients with severe hepatic impairment and therefore its use is not recommended in this patient group. As there is limited experience of use of Edarbi in patients with mild to moderate hepatic impairment close monitoring is recommended and consideration should be given to 20 mg as a starting dose.

For patients with possible depletion of intravascular volume or salt depletion (e.g. patients with vomiting, diarrhoea or taking high doses of diuretics), Edarbi should be initiated under close

medical supervision and consideration can be given to 20 mg as a starting dose.

Caution should be exercised in hypertensive patients with congestive heart failure as there is no experience of use of Edarbi in these patients.

No dose adjustment is required in the black population, although smaller reductions in blood pressure are observed compared with a non-black population. This generally has been true for other angiotensin II receptor (AT1) antagonists and angiotensin-converting enzyme inhibitors. Consequently, uptitration of Edarbi and concomitant therapy may be needed more frequently for blood pressure control in black patients.

**Contraindications:**
Hypersensitivity to the active substance or to any of the excipients, second and third trimester of pregnancy is contraindicated.

**Precautions:**
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with congestive heart failure, severe renal impairment or renal artery stenosis), treatment with medicinal products that affect this system, such as angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists, has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with Edarbi.

Caution should be exercised in hypertensive patients with severe renal impairment, congestive heart failure or renal artery stenosis, as there is no experience of use of Edarbi in these patients.

Excessive blood pressure decreases in patients with ischaemic cardiomyopathy or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

There is currently no experience on the use of Edarbi in patients who have recently undergone kidney transplantation.

Edarbi has not been studied in patients with severe hepatic impairment and therefore its use is not recommended in this patient group.

In patients with marked volume- and/or salt-depletion (e.g. patients with vomiting, diarrhoea or taking high doses of diuretics) symptomatic hypotension could occur after initiation of treatment with Edarbi. Hypovolemia should be corrected prior to administration of Edarbi, or the treatment should start under close medical supervision, and consideration can be given to a starting dose of 20 mg.

Patients with primary hyperaldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of Edarbi is not recommended in these patients.

Based on experience with the use of other medicinal products that affect the renin-angiotensin-aldosterone system, concomitant use of Edarbi with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (e.g. heparin) may lead to increases in serum potassium in hypertensive patients (see section 4.5). In the elderly, in patients with renal insufficiency, in diabetic patients and/or in patients with other co-morbidities, the risk of hyperkalaemia, which may be fatal, is increased. Monitoring of potassium should be undertaken as appropriate.

Special caution is indicated in patients suffering from aortic or mitral valve stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.
As with other angiotensin II receptor antagonists the combination of lithium and Edarbi is not recommended.

**Drug Interactions:**
During concurrent use of lithium and angiotensin-converting enzyme inhibitors, reversible increases in serum lithium concentrations and toxicity have been reported. A similar effect may occur with angiotensin II receptor antagonists. Due to the lack of experience with concomitant use of azilsartan medoxomil and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

When angiotensin II receptor antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II receptor antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, adequate hydration and monitoring of renal function at the beginning of the treatment are recommended.

Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products (e.g. heparin) may increase potassium levels. Monitoring of serum potassium should be undertaken as appropriate.

No clinically significant interactions have been reported in studies of azilsartan medoxomil or azilsartan given with amlodipine, antacids, chlortalidone, digoxin, fluconazole, glyburide, ketoconazole, metformin, and warfarin.

Azilsartan medoxomil is rapidly hydrolysed to the active moiety azilsartan by esterases in the gastro intestinal tract and/or during drug absorption. In vitro studies indicated that interactions based on esterase inhibition are unlikely.

**Side Effects:**
Dizziness and diarrhoea.

**Forensic Classification:**
P1S1S3

# Break the Cycle of Conventional Therapy

NEW

*AFINITOR is the* ***FIRST and ONLY Targeted Therapy***
*to enhance and to extend the clinical benefits of endocrine therapy in patients with HR-positive, HER-negative advanced breast cancer progression*

## *Significant durable PFS benefits after First Recurrence on NSAI Adjuvant Treatment*

## *– Afinitor + exemestane vs exemestane alone: 15.2 months vs 4.2 months[1]*

AFINITOR® (everolimus) tablets

NOVARTIS ONCOLOGY

**Novartis Pharmaceuticals (HK) Ltd**
27/F, 1063 King's Road, Quarry Bay, H.K.
Tel: 2882 5222 Fax: 2577 0274

Reference: 1. Campone et al. St. Gallen Breast Cancer Conference 2013. Poster 276

**Further information is available on request**

**Important note:** Before prescribing, consult full prescribing information. **Presentation:** Tablets containing 5 mg or 10 mg of everolimus. **Indications:** Afinitor is indicated for the treatment of • hormone receptor-positive, HER2/neu negative advanced breast cancer (BC), in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor. • unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumors (NET) of pancreatic origin in adults with progressive disease • patients with advanced renal cell carcinoma (RCC), whose disease has progressed on or after treatment with VEGF-targeted therapy. **Dosage:** one 10 mg AFINITOR Tablet once daily. • The once daily dose should be taken orally at the same time every day, either consistently with or consistently without food. The tablets should not be chewed, or crushed. • **Dose adjustment:** Dose adjustment may be required due to adverse drug reactions (ADRs), and hepatic status (Child-Pugh). Afinitor may be dose reduced or temporarily withheld (e.g. for one week) followed by reintroduction at 5 mg daily. If dose reduction is required, the suggested dose is 5 mg daily. • **Children:** safety and efficacy have not been established in children aged 0 to 18 years. • **Patients with hepatic impairment:** recommended dose is 5 mg daily in patients with moderate hepatic impairment (Child-Pugh B). Everolimus has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) and is not recommended for use in this patient population. **Contraindications:** Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients. **Warnings/Precautions:** • **Non-infectious pneumonitis:** Cases have been described in patients taking AFINITOR, some of these have been severe and on rare occasions, a fatal outcome was observed. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic, and other non-medicinal causes have been excluded. In some cases, management of pneumonitis may require interruption or discontinuation of treatment. The use of corticosteroids may be indicated. AFINITOR may be reinitiated at 5 mg daily. • **Infections:** AFINITOR is immunosuppressive. Localized and systemic bacterial, fungal, viral, or protozoal infections (e.g. pneumonia, aspergillosis, candidiasis, and hepatitis B reactivation) have been described in patients taking AFINITOR; some of these have been severe and occasionally fatal. Pre-existing infections should be resolved prior to starting treatment with AFINITOR. Be vigilant for symptoms or signs of infection during treatment with AFINITOR. In case of emergent infections, institute appropriate treatment promptly and consider interruption or discontinuation of AFINITOR. If a diagnosis of invasive systemic fungal infection is made, discontinue AFINITOR and treat with appropriate antifungal therapy. • **Hypersensitivity reactions**, manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain or angioedema, have been observed with everolimus. • **Oral ulceration:** Mouth ulcers, stomatitis, and oral mucositis have been seen in patients treated with AFINITOR. Topical treatments are recommended, but alcohol-, hydrogen peroxide, iodine-, or thyme containing mouthwashes should be avoided. Antifungal agents should not be used unless fungal infection has been diagnosed. • **Renal failure:** Cases of renal failure (including acute renal failure), some fatal, have been observed in patients treated with AFINITOR. Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair their renal function. • **Laboratory tests and monitoring:** Renal function (including blood urea nitrogen, urinary protein or serum creatinine), blood glucose and lipids, and complete blood counts are recommended prior to initiation of and periodically during treatment. • **Carcinoid tumors:** The safety and efficacy of AFINITOR in patients with carcinoid tumors have not been established. • **Hepatic impairment:** Not recommended in patients with severe hepatic impairment (Child-Pugh C). • **Vaccination:** Avoid use of live vaccines during AFINITOR therapy. • **Lactose:** Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take AFINITOR. • **Wound healing complications:** Impaired wound healing is a class effect of rapamycin derivatives, including AFINITOR. Caution should be taken with the use of AFINITOR in the peri-surgical period. • **Pregnancy:** AFINITOR is not recommended in pregnant women. • **Women of childbearing potential:** Use highly effective contraception methods while receiving AFINITOR and for up to 8 weeks after ending treatment. • **Breast-feeding:** Women taking AFINITOR should not breast-feed. • **Fertility:** Male and female fertility may be compromised by treatment with AFINITOR. Menstrual irregularities, secondary amenorrhea, and associated luteinizing hormone (LH) / follicle stimulating hormone (FSH) imbalance have been observed in female patients receiving AFINITOR. **Interactions:** • Avoid concurrent treatment with potent CYP3A4 inhibitors or PgP inhibitors (e.g. ketoconazole, itraconazole, ritonavir, clarithromycin, telithromycin). • Caution with moderate CYP3A4 inhibitors or PgP inhibitors (e.g. erythromycin, verapamil, diltiazem, fluconazole, ciclosporin, amprenavir, fosamprenavir, aprepitant). Consider a dose decrease of AFINITOR when co-administered with moderate inhibitors. • Avoid concurrent treatment with potent CYP3A4 inducers or PgP inducers (e.g. rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, efavirenz, nevirapine, dexamethasone, prednisone, prednisolone,). Consider a dose increase of AFINITOR when co-administered with potent inducers. • Preparations containing St John's Wort should not be used during treatment with AFINITOR. • Avoid grapefruit juice, grapefruit, star fruit, Seville oranges and other foods affecting CYP3A4 or PgP. • Caution when used in combination with orally administered CYP3A4 substrates with a narrow therapeutic index. **Adverse drug reactions:** • **Very common (≥10%):** Infections, anemia, thrombocytopenia, anorexia, hypertriglyceridemia, hyperglycemia, hypercholesterolemia, dysgeusia, headache, pneumonitis, epistaxis, cough, dyspnea, stomatitis, diarrhea, nausea, vomiting, mucosal inflammation, rash, dry skin, pruritus, nail disorder, fatigue, peripheral edema, asthenia, pyrexia, weight decreased. • Common (≥1 to <10%): Neutropenia, leukopenia, lymphopenia, hyperlipidemia, hypocalcemia, hypophosphatemia, diabetes mellitus, hypokalemia, dehydration, insomnia, conjunctivitis, eyelid edema, hypertension, hemorrhage, pulmonary embolism, hemoptysis, dry mouth, abdominal pain, oral pain, dyspepsia, dysphagia, palmar-plantar erythrodysaesthesia syndrome, erythema, skin exfoliation, acneiform dermatitis, onychoclasis, skin lesion, mild alopecia, arthralgia, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood creatinine increased, renal failure, proteinuria, chest pain. • Uncommon (≤1%): Pure red cell aplasia, ageusia, congestive cardiac failure, acute respiratory distress syndrome, flushing, deep vein thrombosis, angioedema, impaired wound healing. • Not known: hypersensitivity. • In clinical trials, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infections is an expected event during periods of immunosuppression. **Packs:** Tab 5mg x 30's, 10mg x 30's. **Legal classification:** P/S1/S4. (ESS version Aug 2012).

HK1309135084

Avamys™
fluticasone furoate

# Avamys™ – effective and consistent relief of NASAL and OCULAR symptoms of allergic rhinitis[1,2]

## Significant reduction by 40.1% in nasal congestion[1], one of the leading causes of impaired sleep in allergic rhinitis patients[3]


## No. 1 Anti-Allergic Rhinitis therapy in Hong Kong[4]

- **GENTLE FINE MIST improves patient experience compared to a conventional nasal spray[5]:**
  - **No smell, with less aftertaste, less drip down the nose or throat**
- **Effectively improves quality of life, including patients' sleep and ability to perform daily activities[6]**
- **Absolute bioavailability is 0.5%, minimizing systemic exposure[7,8]**
- **Indicated for patients as young as 2 years old[7]**

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

**AVAMYS™ NASAL SPRAY Abbreviated Prescribing Information: INDICATIONS** AVAMYS is indicated for the treatment of the symptoms of seasonal and perennial allergic rhinitis in patients 2 years of age and older. **DOSAGE AND ADMINISTRATION** Administer AVAMYS (27.5mcg/spray) by the intranasal route only. Adults & adolescents ≥12 years: The recommended starting dosage is 110mcg (2 sprays in each nostril) once daily. When the symptoms have been controlled, reducing the dosage to 55mcg (1 spray in each nostril) once daily may be effective for maintainence. Children 2-11 years: The recommended starting dosage in children is 55mcg (1 spray in each nostril) once daily. Children not adequately responding to 55mcg may use 110mcg (2 sprays in each nostril) once daily. Once symptoms have been controlled, the dosage may be decreased to 55mcg once daily. **CONTRAINDICATIONS** Hypersensitivity to any of the ingredients. **WARNINGS AND PRECAUTIONS** AVAMYS undergoes extensive first-pass metabolism by CYP3A4, therefore the pharmacokinetics of AVAMYS in patients with severe liver disease may be altered. Co-administration with ritonavir is not recommended. **INTERACTIONS** In a drug interaction study of AVAMYS with the potent CYP3A4 inhibitor ketoconazole there were more subjects with measurable AVAMYS plasma concentrations in the ketoconazole group compared to placebo. The enzyme induction and inhibition data suggest that there is no theoretical basis for anticipating metabolic interactions between AVAMYS and the cytochrome P450-mediated metabolism of other compounds at clinically relevant intranasal doses. Therefore, no clinical studies have been conducted to investigate interactions of AVAMYS on other drugs. **PREGNANCY AND LACTATION** Adequate data are not available regarding the use of AVAMYS during pregnancy and lactation in humans. AVAMYS should be used in pregnancy only if the benefits to the mother outweigh the potential risks to the foetus. Following intranasal administration of AVAMYS at the maximum recommended human dose (110mcg/day), plasma AVAMYS concentrations were typically non-quantifiable and therefore potential for reproductive toxicity is expected to be very low. **ADVERSE REACTIONS** Epistaxis, nasal ulcerations. Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria. Headache. Rhinalgia, nasal discomfort (including nasal burning, nasal irritation and nasal soreness), nasal dryness. **OVERDOSE** Acute overdose is unlikely to require any therapy other than observation. Abridged PI (GDS 07/IPI06)

Please refer to the full prescribing information before prescribing. Full prescribing information is available upon request.
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For adverse events reporting, please call GlaxoSmithKline Limited at 9046 2498.
The material is for the reference and use by healthcare professionals

**REFERENCES: 1.** Vasar M et al. Fluticasone furoate nasal spray: Effective monotherapy for symptoms of perennial allergic rhinitis in adults/adolescents. Allergy Asthma Proc 2008; 29(3): 313–321 **2.** Maspero JF et al. The efficacy of fluticasone furoate on 7 individual nasal and ocular symptoms of seasonal allergic rhinitis. Abstract 524, World Allergy Congress, Buenos Aires, December 2009 **3.** Sardana N et al. Congestion and Sleep Impairment in Allergic Rhinitis. Asian Pac J Allergy Immunol 2011; 29:297–306 **4.** HKAPI, HK Sales data in Class R1A, R1B, R6A, 2011 to Mar 2013 **5.** Meltzer EO et al. Preferences of Adult Patients with Allergic Rhinitis for the Sensory Attributes of Fluticasone Furoate Versus Fluticasone Propionate Nasal Sprays: A Randomized, Multicenter, Double-Blind, Single-Dose, Crossover Study. Clin Ther 2008; 30: 271–279 **6.** Fokkens WJ et al. Once daily fluticasone nasal spray is effective in seasonal allergic rhinitis caused by grass pollen. Allergy 2007; 62:1078–1084. **7.** Avamys Hong Kong Prescribing Information, 2012 **8.** Allen A et al. Absolute bioavailability of intranasal fluticasone furoate in healthy subjects. Clin Ther 2007; 29(7): 1415–1420

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