MADRAC

Malaysian Adverse Drug Reactions Newsletter

National Pharmaceutical Control Bureau,
Ministry of Health Malaysia

This newsletter is also available on our website: http://www.bpfk.gov.my

To report an adverse drug reaction:

1. Visit http://www.bpfk.gov.my,
2. Click on "MADRAC (Adverse Drug Reactions)" on the left toolbar; and
3. Click on "Reporting Online".

Alternatively, please contact:
National Centre for Adverse Drug Reactions Monitoring,
Centre for Post Registration
National Pharmaceutical Control Bureau
Ministry of Health
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SAFETY ISSUES OF CURRENT INTEREST

CHAMPIX® (VARENICLINE) - AN UPDATE

In the 11 November 2008 issue of DIA Daily, it had been reported that up to 29 September 2008, the United Kingdom's Medicines and Healthcare Products Regulatory Agency (U.K. MHRA) received a total of 3541 adverse reactions reports related to varenicline. Since approval of Chantix® (brand of varenicline in the U.K.), 10 people had committed suicide, 213 people had suicidal thoughts and 407 people had depression after taking Chantix®. However, the U.K. MHRA commented that such adverse reactions may be related to other factors such as nicotine withdrawal or concomitant medications.

Up to October 2008, the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) has received 13 adverse drug reactions (ADRs) reports related to varenicline (marketed locally under the brand Champix®). Out of the 13 ADRs reported, 2 reports were related to depression.

- The first report involved a 42 year old male patient who had no prior history or family history of emotional or mental health problems. The patient did not use alcohol and was not on any concomitant medication during his therapy with Champix®. After the first week of therapy with Champix®, the patient felt depressed and attempted suicide. The dosage the patient was taking was 0.5mg twice daily.

- The second report involved a male patient who experienced lost of appetite, depression, sleeping difficulty, feeling hot and epigastric discomfort after taking Champix® 0.5mg twice daily for twelve days.

Local prescribing information has included the occurrence of depression, suicidal ideation and suicide attempt in the "Special Warnings and Precautions for Use" and "Undesirable Effects" sections. However, this information was not clearly stated. After discussions with the Drug Control Authority, Pfizer has agreed that such information should also be clearly and prominently included in the Patient Information Leaflet to warn patients of the possibility of such adverse effects when undergoing treatment with Champix®.

The cooperation of the Malaysian Medical Association (MMA) and the Malaysian Pharmaceutical Society (MPS) have also been sought to highlight and disseminate concerns relating to this safety issue to all their members. MADRAC would like to request that healthcare professionals report any adverse reactions suspected to be associated with Champix® so that the local situation can be more closely monitored.

References:

1. MADRAC's Database.
2. DIA Daily, "U.K. Drug Regulator Links Chantix to Reports of Depression and Suicide", 11 November 2008.

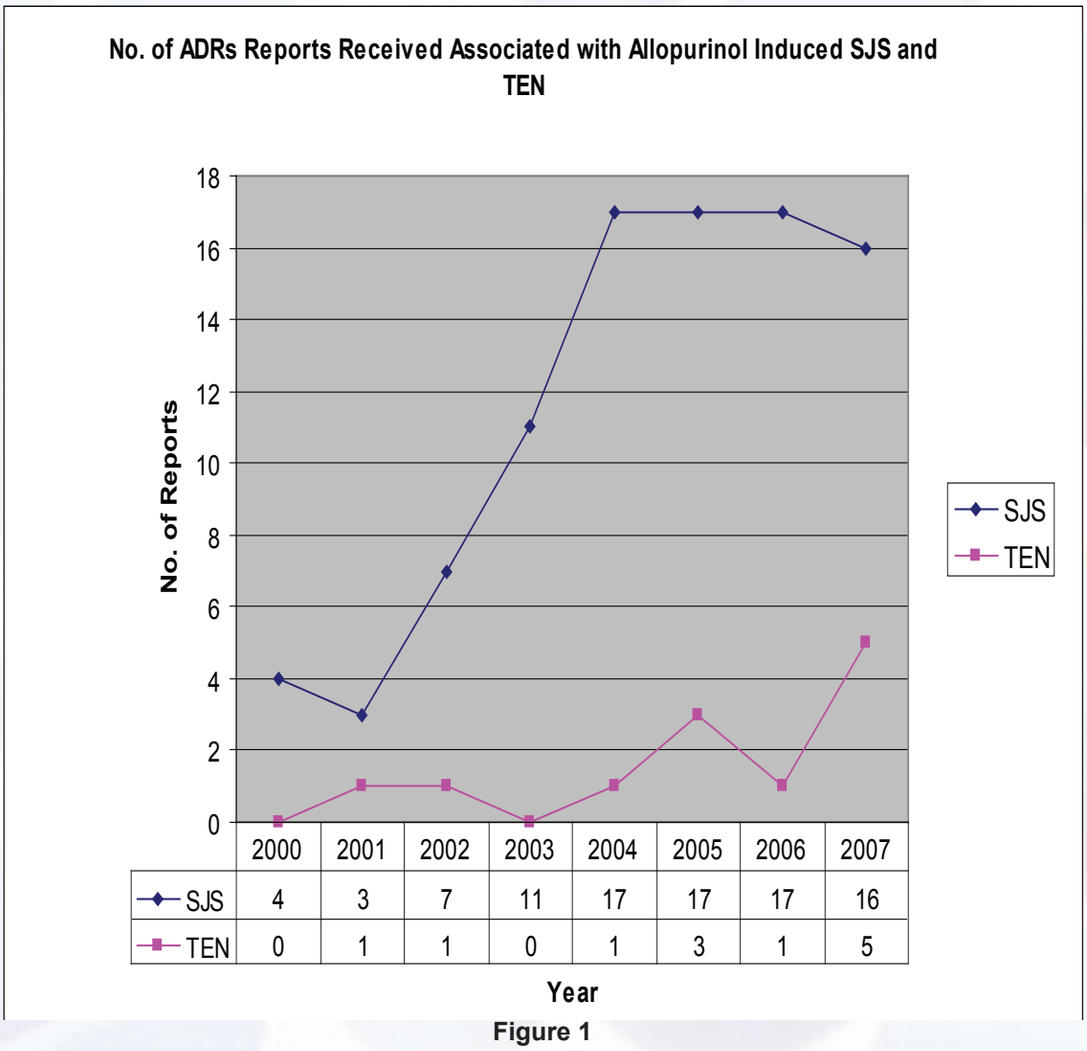
STEVENS JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS ASSOCIATED WITH THE USE OF ALLOPURINOL

Allopurinol works by preventing the formation of uric acid (a protein metabolite that is present in the blood and released in the urine). Due to its capability in blocking uric acid production, it can prevent gout attacks and the formation of kidney stones or other kidney problems. **It is indicated for recurrent gouty arthritis attacks, primary or secondary hyperuricaemia associated with gouty arthritis, uric acid nephropathy and recurrent uric acid stone formation. Allopurinol is not indicated for moderately elevated uric acid or non – gouty arthralgia or arthritis.** It has no pain or anti-inflammatory activity. Therefore it has no value in the treatment of acute gout attacks. It is not indicated for the treatment of asymptomatic hyperuricaemia.

Skin reactions are the most common adverse drug reactions for allopurinol. It may occur at any time during treatment. It may be pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative. Skin reactions can be serious and may lead to life threatening Stevens Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN).

From year 2000 to 2007, the MADRAC received 310 reports of ADRs related to the use of allopurinol. Twelve of the reports involved fatality. Among the adverse reactions reported, 80% were skin reactions, including mild reactions such as rash and itchiness as well as severe life threatening reactions such as SJS and TEN.

Figure 1 shows the number of spontaneous ADR reports MADRAC received from year 2000 to 2007 with allopurinol as the suspected drug and SJS and/or TEN as the ADR(s). However, the figures were obtained from random reporting and are not absolute. Hence, the figures should not be interpreted to imply that there is an increasing trend of SJS and/or TEN associated with allopurinol.



	2000	2001	2002	2003	2004	2005	2006	2007
SJS	4	3	7	11	17	17	17	16
TEN	0	1	1	0	1	3	1	5

Figure 1

As SJS and TEN are life threatening ADRs, the MADRAC would like to remind doctors or prescribers to be more selective before prescribing allopurinol to their patients. The risk benefit profile should be evaluated. For long term control of gout in patients who have frequent attacks, the xanthine oxidase inhibitors like allopurinol may be used to reduce production of uric acid. Treatment for chronic gout should not be started until after an acute attack has completely subsided, usually 2-3 weeks. The initiation of allopurinol treatment may precipitate an acute attack, therefore colchicine or a suitable NSAID should be used as prophylactic and continued for at least one month after hyperuricaemia has been corrected. If an acute attack develops during treatment for chronic gout, then allopurinol should continue at the same dosage and the acute attack should be treated in its own right. Treatment for gouty arthritis must be continued indefinitely to prevent further attacks of gout.

ALLOPURINOL IS NOT INDICATED FOR THE TREATMENT OF ASYMPTOMATIC HYPERURICAEMIA.

References:

1. MADRAC's Database.
2. British National Formulary No. 56, September 2008

ADVERSE EVENTS FOLLOWING IMMUNISATION

Vaccines are biological substances that are used to protect our body from unwanted diseases. Hence, it will have to affect our immune system in order to produce some protective mechanisms. It is no doubt that one may expect adverse events to occur after an immunisation. The severity of adverse events following immunization (AEFIs) is personalised. It is dependent of many factors such as age and concomitant diseases.

The World Health Organization (WHO) classified the AEFIs into five types. These are

1. **Vaccine reaction:** event caused by the underlying properties of the vaccine. This means that the event happened/precipitated because of the vaccine even though the vaccine has been given correctly i.e. correct route of administration and correct dosage.
2. **Programme error:** event caused by an error in vaccine preparation, handling or administration i.e. broken cold chain and wrong site of administration.
3. **Coincidental event:** event happened after immunisation but not caused by the vaccine i.e. chance association.
4. **Injection reaction:** event from anxiety about, pain from, the injection rather than the vaccine.
5. **Unknown:** event in which the cause cannot be determined.

It has always been a challenge giving AEFIs causality grading. This is because the most reliable way to determine if an adverse event is directly related to the vaccine is through randomised controlled trials. Randomised controlled trials are useful in comparing the number of adverse events happening among the vaccinated and non – vaccinated groups. However, there is a limitation in these trials. The number of people enrolled in these trials is not significant enough when it comes to assessing rare AEFIs. This is where post – marketing surveillance plays a role.

Healthcare professionals and the industries are encouraged to report any encountered AEFIs (as well as ADRs related to medicines) to the MADRAC. This is because health regulators, healthcare professionals and the industries are all responsible in playing a role in post – marketing surveillance.

Currently, MADRAC together with the Pharmacy Services Division are actively promoting to all government hospitals and Health Centres to report any AEFIs encountered while giving vaccines. Reporting from the private sector is similarly important.

From year 2000 to November 2008, the MADRAC has received 456 ADRs reports related to the use of vaccines. There were 4 deaths. However, **none** could be considered directly related to the vaccines as there were underlying diseases causing the deaths.

References:

1. Weekly Epidemiological Record, "Causality Assessment of Adverse Events Following Immunization", http://www.who.int/wer, No. 12, 2001, 76, 85 – 92
2. WHO, "Information for Health – Care Workers – Managing Adverse Events", http://www.who.int/immunization_safety/aefi/managing_AEFIs/en/print.html, 2008.
3. MADRAC's Database.

REGULATORY MATTERS

ACOMPLIA® (RIMONABANT)

Acomplia® contains the active ingredient rimonabant and it is indicated as a drug therapy adjunct to diet and exercise for the treatment of obese patients (BMI ≥ 30 kg/m2), or overweight patients (BMI > 27 kg/m2) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia.

Rimonabant is a selective cannabinoid-1 receptor (CB1) antagonist that inhibits the pharmacological effects of cannabinoid agonists. The endocannabinoid system is a physiological system present in the brain and peripheral tissues (including adipocytes) that affects energy balance, glucose and lipid metabolism and body weight, and in neurons of the mesolimbic system, modulates the intake of highly palatable, sweet or fatty foods.

Situation in European Union (EU)

Acomplia® was first registered in the EU in June 2006 and psychiatric adverse events such as depressive disorders have been included in the prescribing information ever since it was registered. Since then, the EU's Committee for Medicinal Products for Human Use (CHMP) has been monitoring the product and updating the prescribing information when new information was available.

Since registration, the prescribing information has been updated twice. The first update in July 2007 was to include a contraindication for patients with ongoing major depressive illness and/or ongoing antidepressive treatment and also to warn that treatment with Acomplia® should be ceased if a patient develops depression. The second update in May 2008 was to allow a better understanding of the time of onset of depressive reactions and reinforce existing warnings related to psychiatric disorders especially depression. A Dear Healthcare Professional Letter (DHCP) was circulated in mid-July 2008 to inform prescribers to actively monitor for signs and symptoms of psychiatric disorders especially depression after initiation of therapy.

However, during the CHMP's meeting on the 20 – 23 October 2008, it was recommended that the marketing authorisation of Acomplia® be suspended. This was because after evaluating post – marketing adverse reactions reports received by the CHMP and safety data from Sanofi – Aventis, the CHMP decided that its risks outweigh the benefits.

Situation in Malaysia

Acomplia® was registered in Malaysia since September 2007. When it was registered in Malaysia, the product's prescribing information incorporated all of CHMP's first recommended update (July 2007). Sanofi – Aventis also updated the local prescribing information and issued a DHCP letter in July 2008 following CHMP's second recommendation (May 2008).

When CHMP recommended that the marketing authorisation of Acomplia® was to be suspended in October 2008, Sanofi – Aventis also voluntarily suspended marketing of Acomplia® and recalled all batches of Acomplia® locally. A "Dear Doctor" letter was issued to respective doctors to inform of this decision on the 28 October 2008. In the letter, doctors were also advised as follows;-

i. Not to issue or renew any prescription for Acomplia®;
ii. To invite patients to contact their prescribers if they were involved in clinical trials with Acomplia®;
iii. Patients do not need to stop taking Acomplia® immediately but patients who wish to stop can do so at any time.

Since registration of Acomplia®, the MADRAC has received a total of twelve ADRs reports. All patients except two had concomitant medications. Adverse reactions involved were cracked lips, dry mouth, headache, anger, agitation, bad mood, palpitation, vomiting, dizziness, fear, shortness of breath, tiredness, anxiety, aggressiveness, mood swings, increase in appetite, concentration impaired and nausea.

Recently, on the 12 November 2008, Sanofi – Aventis has requested for a voluntary suspension of the registration of Acomplia® and suspended all ongoing clinical trials.

References:

1. European Medicines Agency, "Press Release: The European Medicines Agency recommends suspension of the marketing authorization of Acomplia", 23 October 2008.
2. MADRAC's Database.
3. Sanofi – Aventis's Letter on "Acomplia – Stopping of Marketing and Sales Activities in Malaysia".
4. Sanofi – Aventis's Letter on "Acomplia – Voluntary Suspension of Registration".

FLUOROQUINOLONES AND TENDON DISORDERS

Fluoroquinolone antimicrobials are broad spectrum antimicrobials that have *in vitro* activity against a wide range of Gram – positive and Gram – negative organisms. The bactericidal action of fluoroquinolone antimicrobials are through inhibition of bacterial type II topoisomerases (DNA gyrase and topoisomerase IV). DNA gyrase and topoisomerase IV are enzymes which are responsible for bacterial DNA replication, transcription, repair, and recombination.

Although tendon disorders such as tendonitis and tendon rupture were documented as 'very rare', these were well known ADRs when being associated with fluoroquinolone antimicrobials. Based on the report done by the United States Food and Drug Administration (USFDA), the risk of developing fluoroquinolone – associated tendonitis and tendon rupture was higher in patients older than 60 years old, patients who were taking corticosteroids and kidney, heart and lung transplant patients.

Though tendonitis and tendon rupture were documented in the prescribing information leaflet, the USFDA continued to receive a high number of ADRs. Similarly, the Australian Therapeutic Goods Association (TGA) mentioned that they continued to receive ADRs on fluoroquinolones – associated tendonitis and tendon rupture despite reminders in bulletins and alerts.

In Malaysia, there are 120 products registered by the DCA which contain the following fluoroquinolone antimicrobial:-

Ciprofloxacin	Norfloxacin	Lomefloxacin
Levofloxacin	Ofloxacin	
Moxifloxacin	Pefloxacin	

There are 36 products undergoing evaluation which contain:-

Ciprofloxacin	Levofloxacin	Ofloxacin
Gemifloxacin	Lomefloxacin	Pefloxacin
Grepafloxacin	Norfloxacin	Sparfloxacin

From year 2000 to October 2008, MADRAC received a total of 150 ADRs reports. There was only one report in which the patient experienced "tendonitis" and "convulsions grand mal" after taking pefloxacin 400 mg twice daily for three days. Pefloxacin was indicated for her urinary tract infection. Her past medical history included an episode of febrile fits during her childhood.

The MADRAC would like to remind medical prescribers to weigh the risks and benefits before prescribing fluoroquinolone antimicrobials to patients older than 60 years old, patients who are taking corticosteroid drugs and kidney, heart and lung transplant patients. Healthcare professionals must play a role in patient counseling; advising patients who experienced pain, swelling and inflammation of a tendon or tendon rupture to stop taking their fluoroquinolone antimicrobial therapy and inform their medical prescribers promptly for an alternative therapy. Patients should also be advised to avoid exercising and using the affected area at first sign of tendon pain, swelling and/or inflammation.

The DCA has decided that all products containing a fluoroquinolone antimicrobial must have the following statement in the section "Special Warnings and Precautions for Use" of the product information leaflet:-
Musculo-skeletal system:

"The risk of developing fluoroquinolone-associated tendonitis and tendon rupture is further increased in people older than 60, in those taking corticosteroid drugs, and in kidney, heart, and lung transplant recipients. Patients experiencing pain, swelling, inflammation of a tendon or tendon rupture should be advised to stop taking their fluoroquinolone medication (to specify the active ingredient) and to contact their healthcare professional promptly about changing their antimicrobial therapy. Patients should also avoid exercise and using the affected area at the first sign of tendon pain, swelling, or inflammation"

References:

1. Medwatch, USFDA, http://www.fda.gov/cder/drug/InfoSheets/HCP/fluoroquinolonesHCP.htm, 8 July 2008.
2. Australian Adverse Drug Reactions Bulletin, "Fluoroquinolone antibiotics and tendon disorders: still a problem", Volume 27, Number 5, October 2008.
3. MADRAC's Database.

LOCAL CASE REPORTS

MENTALK CANDY

Mentalk Candy is in the form of a sweet claimed to have health benefits. It was believed to be widely available in our market through direct selling and the internet. The Pharmaceutical Services Division (PSD), Ministry of Health has done laboratory analysis on Mentalk Candy and found that it was adulterated with Aminotadalafil. Similarly, Mentalk Candy was also featured in a report by the Singapore's Health Sciences Authority (HSA) to be adulterated with Aminotadalafil.

Tadalafil is registered in Malaysia and is indicated for the treatment of erectile dysfunction in adult males. It is not indicated to be used by women. This medicine is safe for the indicated usage under the supervision of a registered medical practitioner. However, Aminotadalafil is a new chemical entity that has never been registered in Malaysia. Therefore, its safety profile has never been tested clinically. Mentalk Candy was believed to be marketed for erectile dysfunction. Aminotadalafil can give rise to serious adverse events such as heart failure and depression. Long term consumption and excessive amounts can lead to blindness.

From May to July 2008, there were four ADRs reports associated with the use of Mentalk Candy received by MADRAC.

The first report was received in May in which a 45-year-old male developed jaundice, gastrointestinal haemorrhage and hepatic encephalopathy after ingesting five units of Mentalk Candy in one week. Labarotary investigations indicated deranged liver function tests (LFTs) (none specified) and a low haemoglobin level. Patient was then given supportive treatment and monitored but had not yet recovered at the time of reporting.

The second case was that of a 52-year-old male who took six units of Mentalk Candy in approximately one week. Patient's LFTs were deranged (none specified) and he developed jaundice, acute liver impairment, mild renal impairment associated with fever, chills and rigors. Supportive treatment was given, and parameters on liver and renal function were also monitored. This patient had not recovered at time of reporting.

In addition, a 56-year-old lady with no known underlying disease was reported to have consumed approximately 1 to 2 units of Mentalk Candy daily to improve her vitality. Patient was not on any concomitant medication and was diagnosed by a specialist as having acute hepatitis after consuming Mentalk Candy for approximately one month. This was supported by laboratory investigations that showed her markedly raised LFTs (none specified). The doctor suspected Mentalk Candy as the cause and the patient discontinued taking it. The patient had not recovered at the time of reporting.

The fourth reported case involved a 58-year-old male with no known concomitant disease and medication, who consumed one candy for his general well being. After eight hours, the patient developed high grade fever, tachycardia and walking difficulty. Patient was then sent to the hospital for treatment and rested for two hours before recovering.

Issues concerning food products mixed with a sex stimulant are on the rise. Adulterants are added in food products to avoid detection by the authority. This is also to mislead the public to believe that the product is safe for consumption and can be consumed without limitations. It is advised not to consume Mentalk Candy and to report to the authority if this product is still available in the market. MADRAC will continue to monitor ADRs associated with this product and will cooperate with PSD pertaining to this matter.

References:

1. MADRAC's Database
2. Press Statement by PSD on "Mentalk Candy Adulterated with Sex Stimulant Agent" 6 June 2008 available at http://www.pharmacy.gov.my/