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MADRAC

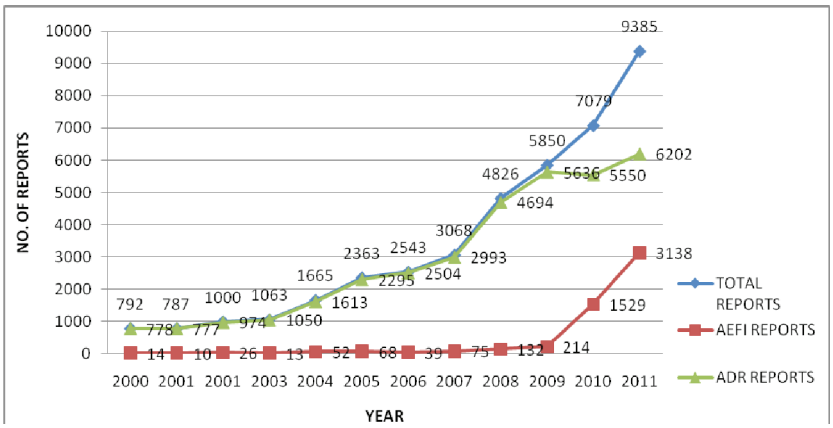
Malaysian Adverse Drug Reactions Newsletter
National Pharmaceutical Control Bureau, Ministry of Health Malaysia
This newsletter is also available on our website: http://www.bpfk.gov.my

ACTIVITIES OF MALAYSIAN ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (MADRAC) FOR 2011

SUSPECTED ADVERSE REACTIONS REPORTED FOR 2011: AN OVERVIEW

A total of **9,385** reports were received in year **2011**, the highest record achieved since year 2000. This figure is a **32.6%** increase from year 2010 and projected to continue in an ascending trend this year. 34% were of Adverse Events Following Immunisation (AEFI) reports whereas the remaining 66% represented all other categories (*please refer to Chart 1*).

Chart 1: Suspected Adverse Reaction Reports Received (Year 2000-2011)



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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 of Products
National Pharmaceutical Control Bureau
Ministry of Health
Peti Surat 319, Jalan Sultan,
46730 Petaling Jaya,
Selangor.

Tel : +603-7883 5400
Fax : +603-7956 7151

Editorial Staff

The increment is mainly contributed by the Ministry of Health's National Immunisation Programme for Human Papilloma Virus (HPV) Vaccines and continuous promotional activities and educational sessions for healthcare professionals conducted in the Ministry of Health's facilities.

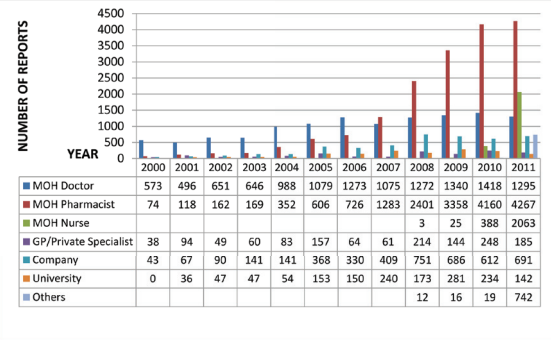
ADR Reporters - 7,625 reports (81.3%) were sent in by healthcare professionals from the Ministry of Health. This is an increase from last year's record of 5,966 reports. Year 2011 also showed an increase (12.9%) in the number of ADR reports from the Marketing Authorisation Holders (MAH) compared to year 2010. However, there was a dip of 25% in reports from GP/private specialists. The Others category of reporters comprised of other healthcare professionals, consumers, retail pharmacist reports as well as reports of unknown designations.

ADR Reports by System Organ Class (SOC) - Overall, there were 17,729 suspected adverse events. Excluding application site disorders,classification of all reports according to SOC indicated that most adverse events reported were of the '*Skin and Appendages Disorders'* SOC (17.3%) followed by '*Central and Peripheral Nervous System Disorder'* SOC (13.8%) and '*Body as a Whole – General Disorders'* SOC (13.5%) (*please refer to Chart 3*).

ADR Reports by Pharmacological Groups - The reports received involved 10,202 suspected products, of which 9,500 (93.1%) were mainly prescription products and 460 (4.5%) were non-prescription products. Out of the total, 36.2% reported suspected drugs from the following 3 pharmacological groups i.e. *Cardiovascular* (16.2%), *Anti-infective* (13.8%) and *Analgesic* (6.2%) (*please refer to Chart 4*). This trend is the same as the previous year 2010.

ADR Reports by Age - From the total of 9,385 reports received, the majority of reports (3,720; 39.6%) were from the age group of 18-60 years followed by the elderly group (>60 years of age) which amounted to 1,523 reports (16.2%). There were 558 reports for children less than 12 years of age(5.9%) and 3,047 reports (32.5%) for adolescent in the 12-18 years of age group. However there were also 537 reports of unknown age (5.7%).

Chart 2: Suspected Adverse Reaction Reports According To Reporter (Year 2000-2011)



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
MOH Doctor	573	496	651	646	988	1079	1273	1075	1272	1340	1418	1295
MOH Pharmacist	74	118	162	169	352	606	726	1283	2401	3358	4160	4267
MOH Nurse									3	25	388	2063
GP/Private Specialist	38	94	49	60	83	157	64	61	214	144	248	185
Company	43	67	90	141	141	368	330	409	751	686	612	691
University	0	36	47	47	54	153	150	240	173	281	234	142
Others									12	16	19	742

Chart 3: Top 10 System Organ Class of Suspected Adverse Reactions Reported (2011)

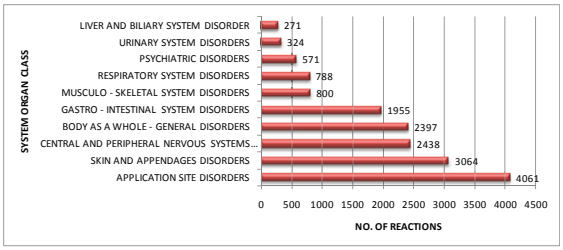
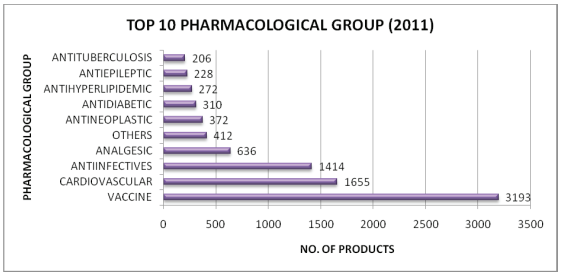


Chart 4: Top 10 Pharmacological Groups of Suspected Adverse Reactions Reported (2011)



ADVERSE EVENTS FOLLOWING IMMUNISATION (AEFI) REPORTING FOR 2011: AN OVERVIEW

By Nurul Huda Hamdan

The National Centre for Adverse Drug Reaction (ADR) Monitoring, National Pharmaceutical Control Bureau (NPCB) is responsible to collect, monitor and analyse all ADR reports involving any pharmaceutical products including vaccines which are in line with the Control of Drugs and Cosmetic Regulations 1984 under the Sale of Drugs Act 1952 (Revised 1989) to ascertain that all the products that registered to NPCB are safe, quality and efficacious to be used.

As of December of 2011, NPCB has received a total of 3,183 Adverse Event Following Immunisation (AEFI) reports. This showed a marked increase of 52% in the number of AEFI reports compared to year 2010. Out of this total, 3,031 reports (95%) were Human Papillomavirus (HPV) vaccine and 152 reports (5%) involved other than HPV vaccine.

Adverse Event Following Immunisation (AEFI) of Human Papillomavirus (HPV)

Following the implementation of the National HPV Immunisation Program to 13 year old girls, a simplified form (*Borang Pemantauan Kesan Sampingan Ringan Selepas Pelalian*) for mild AEFI has been introduced to facilitate the reporting of adverse events by the teenagers or their guardians in an effort to improve AEFI reporting. For the national HPV vaccination program, active surveillance is instituted whereby each of the teenage girls receiving the vaccine will be provided with the simplified form for them to report any adverse events experienced following immunisation.

In year 2011, 3,026 reports were received for Cervarix® and 5 (five) for Gardasil®. The large number of reports received for Cervarix® commensurate with its use as the sole HPV vaccine supplied under the National HPV Vaccination Program.

Under the category of reporters, the largest percentage was by nurses (67.9%), followed by pharmacists (26.0%) and medical officers (3.0%). The nurses contributed to the largest percentage as reporters considering their major role in the special school team administering vaccines to the teenagers.

For the age category, the highest percentage of patients who experience AEFI was the category of 12-17 years of age, which is 91.6%, while another 8% of reports did not specify the age of the vaccine recipient.

Most of the adverse events reported occurred within 3 days after the administration of HPV injection (64%). There were 33% of the reports with the unknown onset time. However, for these cases, majority of the reported adverse events were mild.'

A total of 7,162 adverse events were reported for HPV vaccines. The majority or 55% of the reported adverse events were in the 'Application Site Disorders' System Organ Class (SOC). The most reported adverse events for this class were *injection site pain* (54%), followed by *injection site swelling* (27%) and *injection site erythema* (12%). The top 5 SOC with the most commonly reported adverse events for each SOC are as shown in Table 1.

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Table 1: Top 5 System Organ Class of Suspected Adverse Reactions Reported for HPV Vaccines

NO	*SYSTEM ORGAN CLASS (SOC)* (%)	TOTAL
1.	***APPLICATION SITE DISORDERS (55%)*** - *INJECTION SITE PAIN (54%)* - *INJECTION SITE SWELLING (27%)* - *INJECTION SITE ERYTHEMA (12%)*	3929
2.	***CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS (13%)*** - *DIZZINESS (49%)* - *HEADACHE (45%)*	925
3.	***BODY AS A WHOLE - GENERAL DISORDERS (10%)*** - *WEAKNESS GENERALISED (56%)* - *FEVER (40%)*	752
4.	***GASTRO-INTESTINAL SYSTEM DISORDERS (9%)*** - *NAUSEA (52%)* - *VOMITING (47%)*	626
5.	***MUSCULO-SKELETAL SYSTEM DISORDERS (8%)*** - *BODY ACHING (55%)* - *LIMB WEAKNESS (37%)*	572

NPCB had received 1 serious report with the event of haematuria relating to HPV vaccine. However, investigations conducted did not show any causal relationship between the event and the vaccine.

AEFIs For Other Vaccines

For vaccines other than HPV, the majority of adverse events reported were in the 'Body as a Whole - General Disorders' SOC (22.3%), followed by the 'Central and Peripheral Nervous System Disorders' SOC (18.2%) and the 'Skin and Appendages Disorders' SOC (16.4%).

There were seven serious cases reported to NPCB with the events *fever, fits not otherwise specified (NOS)* and *herpes zoster*. There were also 2 cases reported on *infection streptococcal* and *collapsed, limb stiffness* and *breathing difficult* where both patients succumbed to the condition. The investigations conducted on all of the reports also revealed that the results did not show any causal relationship between the event and the vaccines.

Conclusion

In year 2011, most commonly reported adverse events for HPV vaccine were mild. The trend and types of adverse events reported was quite similar to that of year 2010. year 2010. Although there were serious cases reported for HPV and other vaccines as well, there is no evidence that the safety issue was associated to vaccines or any issue relating to the quality of the vaccines. Hence, throughout the year 2011, there was no regulatory action taken against any vaccines used in Malaysia.

The benefit-risk ratio for HPV vaccines remains positive and NPCB will continue to monitor its safety profile.

SUMMARY OF MADRAC RECOMMENDATIONS FOR REGULATORY ACTIONS BY THE DRUG CONTROL AUTHORITY (DCA): YEAR 2011

During the course of year 2011, the following regulatory actions were proposed by MADRAC and approved by the DCA. These are major directive actions directed by the DCA on certain pharmaceutical products following alerts received from other international regulatory agencies as well as data from local institutions.

Table 2: MADRAC Recommendations for Regulatory Actions by DCA (2011)

No.	Products Involved	Description	MADRAC Meeting	DCA Meeting
1	All antipsychotic drugs	**Class labelling updates regarding use during pregnancy & potential risk to newborns** • Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. • These complications vary in severity. In some cases, neonates required intensive care unit support and prolonged hospitalisation. • Antipsychotic drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.	120 (24/3/11) & 121 (19/5/11)	240 (26/5/11)
2	All beta agonists	**Strengthened warnings against use in preterm labour** • Serious adverse reactions including death have been reported after administration of terbutaline/salbutamol to women in labour. • In the mother, these include increased heart rate, transient hyperglycaemia, hypokalaemia, cardiac arrhythmias, pulmonary oedema and myocardial ischaemia. • Increased foetal heart rate and neonatal hypoglycaemia may occur as a result of maternal administration.	120 (24/3/11) & 122 (21/7/11)	242 (28/7/11)

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No.	Products Involved	Description	MADRAC Meeting	DCA Meeting
3	All 5-alpha reductase inhibitors (5-ARIs)	**Class labelling updates to warn about potential risk of high grade prostate cancer** • Men aged 55 and over with a normal digital rectal examination and PSA ≤3.0 ng/mL at baseline taking finasteride 5 mg/day in the 7-year Prostate Cancer Prevention Trial (PCPT) had an increased risk of Gleason score 8-10 prostate cancer. • Similar results were observed in a 4-year placebo-controlled clinical trial with dutasteride. • However, whether the effect of 5-ARIs to reduce prostate volume, or study-related factors impacted the results of these studies, have not been established.	122 (21/7/11)	242 (28/7/11)
4	All products containing fluoroquinolones	**Class labelling updates to include warning of exacerbation of myasthenia gravis** • Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. • Postmarketing serious adverse events, including deaths and requirement for ventilator support have been associated with fluoroquinolones use in persons with myasthenia gravis. • Avoid fluoroquinolones in patients with known history of myasthenia gravis.	122 (21/7/11)	242 (28/7/11)
5	All products containing ketoconazole	**Contraindication & boxed warnings for risk of serious hepatotoxicity** • Contraindicated in patients with acute or chronic liver disease. • Very rare cases of serious hepatotoxicity, including cases with a fatal outcome or requiring liver transplantation have occurred with the use of oral ketoconazole. Some of these cases occurred within the first month of treatment, including some within the first week. • Assess liver function, prior to treatment to rule out acute or chronic liver disease, and monitor at frequent and regular intervals during treatment, and at the first signs or symptoms of possible hepatotoxicity.	122 (21/7/11)	243 (25/8/11)

SUMMARY OF MADRAC RECOMMENDATIONS FOR SAFETY CHANGES: YEAR 2011

The following regulatory actions were taken upon the recommendations of MADRAC. Please refer to the latest package inserts for complete information.

Table 3: MADRAC Recommendations for Safety Changes (2011)

No.	Products Involved	Recommendations	MADRAC Meeting
1	Avastin (bevacizumab)	**Removal of breast cancer indication for the combination with docetaxel** • The combination of Avastin with docetaxel has been removed from the list of approved indications, as review showed that the benefits of this combination no longer outweigh its risk for the treatment of metastatic breast cancer. • Avastin in combination with paclitaxel continues to be an approved treatment option and is indicated as first-line treatment for patients with metastatic breast cancer.	119 (9/2/11)
2	Multaq (dronedarone hydrochloride)	**Updates to the warning on drug-induced hepatotoxicity** • Hepatocellular liver injury, including life-threatening acute liver failure, has been reported in the postmarketing setting. • Liver function tests should be performed prior to initiation of treatment with dronedarone, after one week and after one month following initiation of treatment and repeated monthly for 6 months, at months 9 and 12, and periodically thereafter. • Patients should immediately report any symptoms of potential liver injury (e.g. sustained new onset abdominal pain, anorexia, nausea, vomiting, fever, malaise, fatigue, jaundice, dark urine or itching) to their physician. **Updates to the warnings of increased risk of serious cardiovascular events in patients with permanent AF** • Multaq is now indicated for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF). • Multaq should not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure. • It is also contraindicated in permanent AF with an AF duration ≥6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician.	119 (9/2/11) 123 (6/10/11)

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No.	Products Involved	Recommendations	MADRAC Meeting
3	Mabthera (rituximab)	**Updates to the warnings on fatal infusion-related reactions in patients with rheumatoid arthritis** • Premedication consisting of analgesic/anti-pyretic (e.g. paracetamol) and an antihistaminic drug (e.g. diphenhydramine) should always be administered before each infusion of rituximab. • Premedication with glucocorticoids should also be administered in order to reduce the frequency and severity of infusion related reactions. • Patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions should be closely monitored.	122 (21/7/11)
4	Aclasta (zoledronic acid)	**Contraindication in severe renal impairment** • The warning of not to be used in patients with severe renal impairment (CrCl<35ml/min) is now being elevated to a contraindication. • Renal impairment has been observed in patients after a single administration and renal failure requiring dialysis or with a fatal outcome has rarely occurred. • Risk factors include advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy or dehydration occurring after Aclasta administration. • A single dose of Aclasta should not exceed 5 mg and the duration of infusion should not be less than 15 minutes.	124 (15/12/11)
5	Pradaxa (dabigatran etexilate)	**Updates on risk of fatal bleeding** • Although rare in frequency in clinical trials, major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes. • Risk factors include advanced age, moderate renal impairment, prior history of bleeding, low body weight, concomitant treatment with other antithrombotic and presence of oesophagitis/ gastritis/gastroesophageal reflux requiring treatment. • Kidney function should be assessed in all patients prior to beginning Pradaxa therapy. Patients with severe kidney impairment (CrCl<30ml/min) should not take Pradaxa. • In elderly patients (>75 years) or in patients with moderate kidney impairment, kidney function should be assessed at least once a year. • Dear Healthcare Provider Communication (DHPC) disseminated.	124 (15/12/11)

REGULATORY MATTERS

PROTAXOS (STRONTIUM RANELATE): NEW CONTRAINDICATIONS IN VENOUS THROMBOEMBOLIC EVENTS (VTE) & REVISED WARNINGS ON SERIOUS SKIN REACTIONS

By Lee Sing Chet

Protaxos (strontium ranelate), an anti-osteoporotic drug, is now contraindicated in current or previous venous thromboembolic events (VTE), including deep vein thrombosis and pulmonary embolism. In addition, warnings on life-threatening skin reactions including Steven-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis(TEN) and Drug Rash With Eosinophilia And Systemic Symptoms (DRESS) have been strengthened to include the signs and symptoms of SJS, TEN and DRESS, as well as their time-to-onset.

In August 2011, a published French study analysing the side effects associated with strontium ranelate identified 199 severe adverse reactions from January 2006 to March 2009. Of it, 52% were cardiovascular (most frequently VTE events, 89%), and 26% were cutaneous. The anti-fractural effect is at least equal to those of bisphosphonates.[1-2]

Local Scenario

In Malaysia, there is only one registered product containing strontium ranelate i.e. Protaxos (granules for oral suspension). Strontium ranelate 2g granules is listed in the Ministry of Health (MOH) Drug Formulary, under category A* (to be initiated by consultant/specialist for for specific indications only).

The National Centre for ADR Monitoring has received 12 reports related to strontium ranelate since year 2000. There are 3 reports of serious skin reaction and 1 report of VTE.

Table 4: Reports of Serious Skin Reaction and VTE for Strontium Ranelate

Adverse Event	Age	Onset	Extent	Outcome (time after diagnosis)
Stevens Johnson syndrome	73	7 weeks	Severe	Not yet recovered (1 week)
	84	7 weeks	Moderate	Not yet recovered (4 days)
	63	5 weeks	Severe	Not yet recovered (2.5 weeks)
Deep vein thrombosis	Unknown	Unknown	Unknown	Unknown

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Recommendation

MADRAC in its 126th meeting on April 12, 2012, concluded that the benefits of Protaxos continue to outweigh their risks. Healthcare professionals are reminded to make patients aware of the time-to-onset and likely signs and symptoms of severe skin reactions. Servier Malaysia Sdn Bhd, product holder for Protaxos will update the local package insert with the new contraindication and warnings as follows:

- ***Contraindications***

  Current or previous venous thromboembolic events (VTE), including deep vein thrombosis and pulmonary embolism.

  Temporary or permanent immobilisation due to e.g. post-surgical recovery or prolonged bed rest.

- ***Special Warnings & Precautions for Use***

  Venous thromboembolism
  PROTAXOS is contraindicated in patients with a past history of venous thromboembolic events and should be used with caution in patients at risk of VTE.

  When treating patients over 80 years at risk of VTE, the need for continued treatment with PROTAXOS should be re-evaluated. PROTAXOS should be discontinued as soon as possible in the event of an illness or a condition leading to immobilisation and adequate preventive measures taken. Therapy should not be restarted until the initiating condition has resolved and the patient is fully mobile. When a VTE occurs, PROTAXOS should be stopped.

  Skin reactions
  Life-threatening cutaneous reactions (Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS)) have been reported with the use of PROTAXOS.

  Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS and TEN is within the first weeks of treatment and is usually around 3-6 weeks for DRESS.

  If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) or DRESS (e.g. rash, fever, eosinophilia and systemic involvement such as adenopathy, hepatitis, interstitial nephropathy, interstitial lung disease) are present, PROTAXOS treatment should be discontinued immediately.

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The best results in managing SJS, TEN or DRESS come from early diagnosis and immediate discontinuation of any suspected drug. Early withdrawal is associated with better prognosis. The outcome of DRESS is favourable in most cases upon discontinuation of PROTAXOS and after initiation of corticosteroid therapy when necessary. Recovery could be slow and recurrences of the syndrome have been reported in some cases after discontinuation of corticosteroid therapy.

If the patient has developed SJS, TEN or DRESS with the use of PROTAXOS, PROTAXOS must not be restarted in this patient at any time.

- ***Undesirable Effects***

Skin and subcutaneous tissue disorders

Rare	:	*DRESS*
Very rare	:	*severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome and toxic epidermal necrolysis*

Reference:

1. Ranélate de strontium (Protelos®) :effetsindésirablesrapportés en France [abstract]. Presse Med. 2011; 40(10):e453-e462.http://www.sciencedirect.com/science/article/pii/S075549821100385X [16 March 2012].
2. EMA. Press release. European Medicines Agency confirms positive benefit-risk balance of Protelos/Osseor, but recommends new contraindications and revised warnings. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/03/WC500124206.pdf [16 March 2012]

RASILEZ (ALISKIREN): CONCOMITANT USE WITH ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITOR OR ANGIOTENSIN RECEPTOR BLOCKER (ARB) IN PATIENTS WITH TYPE 2 DIABETES MELLITUS IS CONTRAINDICATED

By Cheah Voon Yuen

Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin. It blocks the conversion of angiotensinogen to angiotensin I and thereby decreases levels of plasma renin activity (PRA), angiotensin I and angiotensin II (a powerful vasoconstrictor). In Malaysia, it is approved for the treatment of hypertension.

On 20th December 2011, Novartis announced the termination of a clinical trial (**ALTITUDE**) that is being conducted with Rasilez (aliskiren).

ALTITUDE (**AL**iskiren **T**rial **I**n **T**ype 2 Diabetes **U**sing Cardio-renal **D**isease **E**ndpoints) is a multi-national, randomised, double-blind, placebo-controlled, Phase III study which investigated aliskiren for more than 1 year in a specific population of patients with type 2 diabetes and renal impairment, who are at high risk of cardiovascular and renal events. In this study, aliskiren was given in addition to optimal cardiovascular treatment including an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) (standard of care treatment).

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The independent Data Monitoring Committee (DMC) overseeing the trial recommended termination of this study because aliskiren was unlikely to show any benefit, and potential safety concerns had been identified in these high-risk patients. Specifically, an increased incidence of non-fatal stroke, renal complications, hyperkalaemia and hypotension was identified after 18-24 months of follow-up.

Local Scenario

There are 6 aliskiren-containing products registered in Malaysia, of which 2 are products under the brand name Rasilez, with only aliskiren as active ingredient, and the remaining 4 are in combination with hydrochlorothiazide (Rasilez HCT). Aliskiren-containing products are not listed in the Ministry of Health (MOH) Drug Formulary.

The National Centre for ADR Monitoring has received 5 reports related to Rasilez since its registration in year 2008 and 1 report for Rasilez HCT since year 2009. None of these reports were any suspected adverse events of stroke, renal complication, hyperkalaemia or hypotension.

Direct Healthcare Professional Communication (DHPC) letter has also been disseminated with regards to this issue. The product holder has revised the local package inserts for Rasilez and Rasilez HCT. New safety information incorporated is as follows:

- ***Dosage & Administration***

  It must not be used in combination with Angiotensin Converting Enzyme Inhibitors (ACEi) or Angiotensin II Receptor Blockers (ARB) in patients with type 2 diabetes mellitus.

- ***Contraindications***

  Concomitant use of aliskiren with ARBs or ACEi in patients with type 2 diabetes mellitus.

- ***Special Warnings & Precautions for Use***

  Patients with diabetes mellitus are at an increased risk of hyperkalaemia during aliskiren therapy.

Reference:

1. Novartis. Notification to health authorities of termination of ALTITUDE study (SPP100E2337). [20 December 2011]
2. Novartis. Additional information on termination of ALTITUDE study (SPP100E2337). [22 December 2011]
3. EMA. Press release. European Medicines Agency starts review of aliskiren-containing medicines following termination of ALTITUDE study: Interim advice while review is ongoing.[22 December 2011]