AUGUST 2010

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

REGULATORY MATTERS

MUCOLYTIC AGENTS: CONTRAINDICATION IN CHILDREN BELOW 2 YEARS OF AGE

In April 2010, The French Health Agency (AFSSAPS) decided to contraindicate the use of mucolytic agents in children below 2 years of age. The products covered by the AFSSAPS decision are those containing carbocisteine, acetylcysteine, essential terebenthine oil, meglumine benzoate or helicidine.

This decision was based on a National Pharmacovigilance Survey on mucolytic agents initiated by AFSSAPS in France in February 2008 where the available pharmacovigilance data indicated the risk of **aggravation of respiratory symptoms** in connection with the use of mucolytic medicinal products in children below 2 years of age.

Situation in Reference Countries

Most package inserts (PI) for mucolytic-containing products registered in the United Kingdom, Ireland, Canada, Australia and New Zealand do not state warnings or contraindications for children below 2 years of age. Only one PI for carbocisteine in Ireland carries the said contraindication.

Local Scenario

There are 97 mucolytic products registered with the Drug Control Authority (DCA) . 35 products contained carbocisteine, methylcarbocisteine (mecysteine) and acetylcysteine. Essential terebenthine oil, meglumine benzoate and helicidine are not registered in Malaysia.

CONTINUE TO NEXT PAGE

CONTENT

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,
P.O. Box 319, Jalan Universiti,
46730 Petaling Jaya,
Selangor.

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

CONTINUE FROM PAGE 1

Out of the 35 products, 24 were approved for use in children and 11 had indications for children below 2 years of age. There is no specific text in the Warnings or Contraindications sections that these products are contraindicated in children below 2 years of age.

Up to May 2010, the National Centre of ADR Monitoring has received 39 reports relating to the use of mucolytics. 20 cases involved carbocisteine, methylcarbocisteine (mecysteine) and acetylcysteine but none involved children.

Actions by DCA

The following changes to the PI of products containing carbocisteine, methylcarbocisteine (mecysteine) and acetylcysteine were proposed by the Malaysian Adverse Drug Reaction Advisory Committee (MADRAC):

> ***CONTRAINDICATIONS***
> *Contraindicated in children below 2 years of age.*

This proposal was approved by the DCA in its 228th meeting on 27 May 2010.

References:

1. Communication with Sanofi Aventis. *Mucolytic Agents Indicated in Children: French Health Agency (AFSSAPS) decision to contraindicate their use in children below 2 years of age.* [28 April 2010]

MEMBERS OF THE MALAYSIAN ADVERSE REACTION ADVISORY COMMITEE (MADRAC) [OCTOBER 2009-SEPTEMBER 2012]

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ARAVA® (LEFLUNOMIDE): BOXED WARNING - RISK OF SEVERE LIVER INJURY

The United States Food & Drug Administration (US FDA) is adding information on severe liver injury to the Boxed Warning of Arava® (leflunomide) to highlight this risk in patients using this drug and how it may be reduced.

This decision was based on the agency's review of adverse event reports which identified 49 cases of severe liver injury, including 14 cases of fatal liver failure, between August 2002 and May 2009.

Although many patients who developed severe liver injury were also taking other drugs that can damage the liver, or had pre-existing liver disease, the US FDA concluded that use of leflunomide was associated with the development of severe liver injury in these patients with them having the greatest risk.

The agency has added the following *Boxed Warning* into Arava® (Leflunomide) package inserts:

BOXED WARNING

- *Patients with pre-existing liver disease should not receive leflunomide.*
- *Patients with elevated liver enzymes (ALT greater than two times the upper limit of normal) should not receive leflunomide.*
- *Caution should be used in patients who are taking other drugs that can cause liver injury.*
- *Liver enzymes should be monitored at least monthly for three months after starting leflunomide and at least quarterly thereafter.*
- *If the ALT rises to greater than two times the upper limit of normal while the patient is on leflunomide – leflunomide should be stopped, cholestryamine washout begun to speed the removal of leflunomide from the body and follow-up liver function tests conducted at least weekly until the ALT value is within normal range.*

Local Scenario

There are 3 leflunomide products registered with the Drug Control Authority (DCA).

NO.	PRODUCT NAME	REG. NO.	HOLDER
1	Arava Tablet 100mg	MAL20001529A	Sanofi-Aventis
2	Arava 10mg Tablet	MAL20001528A	
3	Arava 20mg Tablet	MAL20001527A	

Up to July 2010, a total of 57 reports regarding leflunomide have been received. 14 cases were related to liver and biliary system disorders and 10 out of the 14 patients were taking other drugs that can damage the liver.

Regulatory Actions

Sanofi-Aventis, the product holder for Arava® have been asked to update the local package insert with this additional information and to send a "Dear Healthcare Professional" (DHCP) letter to all healthcare professionals in Malaysia.

References:

1. U.S. Food & Drug Administration. *FDA Drug Safety Communication: Arava (leflunomide): Boxed Warning – Risk of Severe Liver Injuryl*. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm218912.htm. [13 July 2010]

PROMACTA® (ELTROMBOPAG): PORTAL VENOUS SYSTEM THROMBOSES IN STUDY OF PATIENTS WITH CHRONIC LIVER DISEASE

The US FDA and GlaxoSmithKline (GSK) notified healthcare professionals of a new safety finding in patients with thrombocytopenia due to chronic liver disease treated with eltrombopag.

This notification was based on findings in the ELEVATE study, which identified an imbalance of thrombosis of the portal venous system in the patients treated with eltrombopag versus matching placebo.

Promacta® is the registered trademark in the US, whereas in certain European countries and Malaysia, eltrombopag is marketed under the tradename **Revolade®**.

GSK (U.S.) is working with regulatory agencies to include this safety information in the label and a "Dear Healthcare Professional" (DHCP) letter will be issued to disseminate the new information.

Local Scenario

The DCA has registered 2 products containing eltrombopag. These products are not listed in the MOH Drug Formulary.

No.	Product Name	Reg. No.	Product Holder
1	Revolade Film-coated Tablet 25mg	MAL20102010A	GSK
2	Revolade Film-coated Tablet 50mg	MAL20102011A	

The local PIs of these products have already been incorporated with the safety information regarding thromboembolism.

Up to July 2010, no reports regarding the use of eltrombopag have been received.

Feedback from Product Holder

As the current PI of these products have already encompassed this safety information, GSK (M) has developed some **educational materials** to raise the awareness of healthcare professionals of the risks of thromboembolism in thrombocytopenic patients with chronic liver disease, in line with the strategy adopted in the European Union. The Safety Guide will be provided to every Revolade® prescriber upon their initial order.

GSK (M) has also proposed to prepare **Patient User Guides**, as a tool for the healthcare professionals to educate their patients.

References:

1. FDA MedWatch. *Promacta® (Eltrombopag): Portal venous system thromboses in study of patients with chronic liver disease.* http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm211796.htm [12 May 2010]

PROMETHAZINE HYDROCHLORIDE INJECTION: UPDATED INFORMATION ON RESPIRATORY DEPRESSION AND SEVERE TISSUE INJURY

In April 2010, Health Canada notified healthcare professionals and the public of recent changes to the prescribing information for the injectable form of promethazine.

The revised labelling incorporates a *Boxed Warning* to highlight and strengthen the safety information of the drug as below:

WARNINGS AND PRECAUTIONS

Respiratory Depression – Pediatrics
Promethazine hydrochloride injection should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression. Post-marketing cases of respiratory depression, including fatalities, have been reported with use of promethazine in pediatric patients less than 2 years of age. Caution should be exercised when administering promethazine hydrochloride injection to pediatric patients 2 years of age and older (see WARNINGS AND PRECAUTIONS, Respiratory, Respiratory Depression).

Severe Tissue Injury, Including Gangrene
Promethazine hydrochloride injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Irritation and damage can result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration. Adverse reactions include burning, pain, thrombophlebitis, tissue necrosis, and gangrene. In some cases, surgical intervention, including fasciotomy, skin graft, and/or amputation have been required (see WARNINGS AND PRECAUTIONS, Skin, Severe Tissue Injury, Including Gangrene). Due to the risks of intravenous injection, the preferred route of administration of Promethazine hydrochloride injection is deep intramuscular injection. Subcutaneous injection is contraindicated. See DOSAGE AND ADMINISTRATION for important notes on administration.

Local Scenario

The DCA has registered 4 promethazine products in injectable form.

No.	Product Name	Holder
1	Promethazine HCl – Fresenius 50mg/2ml Injection	Averroes Pharmaceutical
2	DBL® Promethazine Hydrochloride Injection BP 50mg/2ml	Hospira
3	Promethazine Hydrochloride Injection BP 50mg in 2ml	Hospira
4	Promethazine HCl Inj 25mg/ml	Unimed

The current PI for all products contain the warning that use of promethazine is contraindicated in children less than two years of age and that intramuscular route is the preferred route of administration. However, only product (2) above emphasizes that caution should be used when administering promethazine in children aged two years or older while none warn about the rare cases of severe tissue damage regardless of the injection site.

From May 2006 to April 2010, the National Centre of ADR Monitoring has received 14 reports with the use of promethazine, 8 of which were related to the injectable form. 12 out of 14 patients recovered without sequelae. One adult patient with mild skin reactions had not recovered at the time of reporting and another infant whom mother received promethazine for sedation had unknown outcome.

Actions by DCA

The DCA in its 228th meeting has instructed that all hospitals and health clinics be notified of this warning. The hospitals and health clinics are also required to increase monitoring activities on the administration of promethazine hydrochloride injection and to report any adverse events to the National Centre of ADR Monitoring.

References:

1. MedEffect Canada. *Updated Safety Information for Promethazine Hydrochloride Injection*. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2010/2010_58-eng.php#note [26 Apr 2010]

PROPYLTHIOURACIL: NEW BOXED WARNING ON SEVERE LIVER INJURY

In April 2010, the US FDA added a Boxed Warning to the label of propylthiouracil to include the information about reports of severe injury and acute liver failure, some of which have been fatal, in adult and pediatric patients using this medication.

This decision was based on FDA's review on post-marketing safety reports of propylthiouracil, as well as meetings with the American Thyroid Association, the National Institute of Child Health and Human Development and pediatric endocrine clinical community.

Local Scenario

BOXED WARNING

Severe liver injury and acute liver failure, in some cases fatal, have been reported in patients treated with propylthiouracil. These reports of hepatic reactions include cases requiring liver transplantation in adult and pediatric patients.

Propylthiouracil should be reserved for patients who cannot tolerate carbimazole/methimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for the management of hyperthyroidism.

Because of the risk of fetal abnormalities associated with carbimazole/methimazole, propylthiouracil may be the treatment of choice when an antithyroid drug is indicated during or just prior to the first trimester of pregnancy (see Warnings and Precautions).

There are currently 3 propylthiouracil products registered with the DCA:

NO.	PRODUCT NAME	REG. NO.	HOLDER
1.	Propyl Tablet 50mg	MAL19930398A	Imeks Pharma
2.	Propylthiouracil Tablet 50mg	MAL20040762A	Ascent Pharmahealth Asia
3.	Propylthiouracil 50mg BP Tablet	MAL19940154A	Ziwell Medical

Only the PIs for items (1) and (2) above contain the warning on the potential for an increase in risk of hepatotoxicity.

Up to April 2010, the National Centre of ADR Monitoring has received a total of 23 ADR reports regarding propylthiouracil use. Most of the ADRs reported were known common side effects from the use of propylthiouracil such as rash, pruritus and alopecia.

Actions by DCA

The MADRAC has proposed for the *Boxed Warning* to be included in the package inserts of all propylthiouracil products. This proposal was approved by the DCA in its 228th meeting on 27 May 2010.

References

1. U.S. Food & Drug Administration. *FDA Drug Safety Communication: New Boxed Warning on severe liver injury with propylthiouracil.* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm209023.htm 21/4/2010.

PROTON PUMP INHIBITORS (PPI): POSSIBLE INCREASED RISK OF FRACTURES

The US FDA has revised the prescription and over-the-counter (OTC) labels for Proton Pump Inhibitors (PPI) to include new safety information about a possible increased risk of fractures of the hip, wrist and spine.

Background

FDA's review of 7 published epidemiological studies found that those receiving high doses of PPI or have been using them for at least one year are at greater risk of hip, wrist and spine fractures.

The key findings in the review are as follows:

- Six reported an increased risk of fractures with the use of PPI.
- Exposure to PPI ranged from a period of 1 to 12 years, depending on the study.
- The emergence of fractures varied among studies, with one study reporting an increase in fractures with use of PPI in the previous year and another study finding an increase after 5 to 7 years of PPI use.
- The increased risk of fractures was primarily observed in older individuals (50 years of age or older).
- Two studies reported an increase in fractures with higher doses of PPI.
- Two studies reported an increase in fractures with longer duration of use.
- One study did not find a relationship between PPI use and fractures. This study limited the study population to those without major risk factors for fracture.

Comment and Recommendation

In summary, the available data suggested:

- A possible increased risk of fractures of the hip, wrist and spine in patients using PPI.
- The increased risk may be dependent upon dose, duration of use, or both.

Although these studies appear well-designed, it is difficult to determine the clinical relevance of the reported findings and at this time, it is still not clear whether the use of PPI is the cause of the increased risk of fractures seen in some epidemiological studies.

Healthcare professionals, when prescribing PPI, should consider whether a lower dose or shorter duration of therapy would adequately treat the patient's condition.

Local Scenario

Up to July 2010, no report of fractures has been received with use of PPI.

Regulatory Actions

The National Centre of ADR Monitoring will continue to monitor this issue and any new information will be disseminated to all healthcare professionals once they are available.

References:

1. FDA MedWatch. *Proton Pump Inhibitors (PPI): Class labeling change.* http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm213321.htm [25 May 2010]

2. FDA MedWatch. *FDA Drug Safety Communication: Possible increased risk of fractures of the hip, wrist and spine with the use of proton pump inhibitors.* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm [25 May 2010]

SAFETY ISSUES OF CURRENT INTEREST

CARBAPENEMS: SUMMARY REPORT

In Malaysia, there are 11 carbapenem products registered with the DCA.

Since year 2001, a total of 248 ADR reports have been received as shown below:

SUBSTANCE	NO. OF REPORTS	NO. OF EVENTS
IMIPENEM	150	256
MEROPENEM	62	105
ERTAPENEM	36	49
DORIPENEM	0	0

Majority of the ADRs reported are from the following system organ class (SOC):

SYSTEM ORGAN CLASS	IMEPENEM	MEROPENEM	ERTAPENEM
Skin & Appendages	64	41	8
Central & Peripheral Nervous System	59	1	3
Liver & Biliary System	30	18	3
Gastro-Intestinal System	20	14	6
Psychiatric	14	3	18
General Disorders	19	9	7

Of the 3 carbapenems, imipenem has the highest number of reports and events compared to meropenem and ertapenem especially in the skin and appendages SOC and the central and peripheral nervous system SOC. [APPENDIX 1]

A large proportion of the events in the Central & Peripheral Nervous System SOC involved convulsions and seizures.

CNS side effects such as myoclonic activity, confusional side effects and seizures as well as skin reactions such as rash, pruritus, urticaria, Stevens-Johnson syndrome (rare) and toxic epidermal necrolysis (rare) are documented in the local product package inserts.

There are 39 ADR reports of seizures received related to usage with imipenem. The reports involved paediatric and elderly patients. Of the patients who experienced seizures during imipenem therapy, 15 (38.4%) had decreased renal function. One possible mechanism of central nervous system (CNS) toxicity is accumulation of the open-lactam metabolite of imipenem, which may have seizure potential (Tse et al,1987).

Imipenem is excreted mainly by the kidneys hence, individualization of the dose of imipenem should be considered for the elderly and patients with impaired renal function in order to reduce the possibility of seizure activity.

There are 18 ADR reports of psychiatric effects received related to ertapenem therapy. Confusion, hallucination and delirum are the adverse effects being reported. Patients with central nervous system disorder will have increased risk to these adverse effects. Therefore, dose adjustment of ertapenem or use of other alternatives should be considered. Other common ADRs reported include:

- **General Disorders** : Fever, chills, rigors
- **Gastro-intestinal system disorders** : Diarrhea, nausea, vomiting
- **Liver & biliary system disorders** : ALT increased, hepatic enzymes increased, jaundice cholestatic, liver function tests abnormal NOS

The National Centre of ADR Monitoring will continue to monitor the adverse drug reactions related to carbapenems and any new information will be disseminated to all healthcare professionals.

It is recommended that all healthcare professionals be aware of any adverse drug reactions that may be related to the use of carbapenems and to report any event to the National Centre of ADR Monitoring.

APPENDIX 1

SOC	ADR	Imipenem		Meropenem		Ertapenem	
		Local	WHO	Local	WHO	Local	WHO
Central & Peripheral Nervous System Disorders	Convulsions	10	146	0	57	2	152
	Convulsions Grand Mal	4	55	0	20	0	22
	Fits NOS	10	-	1	-	0	-
	Tonic/ Clonic Convulsions	8	1	0	2	0	2
	Seizures	7	3	0	18	0	14
	TOTAL	39	205	1	97	2	190
Skin & Appendages System Disorders	Erythema	4	4	1	28	0	1
	Exanthema	3	-	0	-	0	-
	Itching/ Pruritus	7	31	9	72	4	13
	Rash	14	70	9	122	1	27
	Rash Erythematous	6	31	2	58	0	8
	Rash Maculo-Papular	10	82	7	112	1	9
	Skin Peeling	3	0	1	1	0	1
	Stevens Johnson Syndrome	2	4	3	18	1	4
	Toxic Epidermal Necrolysis	1	5	0	26	0	2
	Urticaria	0	26	5	51	0	16
	TOTAL	50	253	37	488	7	81

H1N1 VACCINES - UPDATES

The H1N1 vaccines used in Malaysia are Pandemrix® and Arepanrix®. Up to June 2010, a total of 861 cases and 2531 Adverse Effects Following Immunisation (AEFIs) regarding H1N1 vaccines had been received by MADRAC. Out of the 861 cases, 466 reports were on Pandemrix®, 390 reports on Arepanrix® and 5 reports where the brand was unknown.

The top 5 states which submitted the highest number of reports are as shown below:

STATE	NO. OF REPORTS
Selangor	156
Sabah	141
Perak	138
Melaka	107
WP KL & Putrajaya	92

Most of the AEFIs reported were known common effects:

- **General disorders** : Fatigue, Fever, Flu-like syndrome, Weakness generalized
- **Administration site conditions** : Injection site pain, Injection site swelling
- **Nervous system disorders** : Dizziness, Headache
- **Gastrointestinal disorders** : Diarrhoea, Nausea, Vomiting
- **Musculoskeletal disorders** : Body aching, Joint pain, Myalgia

The incidences for the common AEFIs are shown in the table below:

AEFI	BRAND			
	Arepanrix®	Pandemrix®	Unknown	Total
Injection Site Pain	188	119	1	308
Injection Site Swelling	40	82	2	124
Fever	193	267	5	465
Headache	50	129	2	181
Nausea	21	46	0	67
Body Aching	69	52	0	121
Myalgia	2	60	2	64
Lethargy	31	51	1	83

The serious ADRs reported are as below:

AEFI	No. of Reports		
	Malaysia		WHO
	Pandemrix®	Arepanrix®	
Chest pain	1	7	109
Facial palsy	1	0	25
Syncope	2	2	167
Breath shortness	7	9	400 (dyspnoea)
Loss of consciousness	1	0	17
Black-out (Not Amnesia)	2	0	17 (Loss of Consciousness)
Photophobia	2	0	12
TOTAL	16	18	747

According to the Disease Control Division (Bahagian Kawalan Penyakit), approximately 39,000 vials of H1N1 vaccine have been distributed throughout Malaysia. Out of this total, only 4,600 vials are Pandemrix® while the remaining 34,400 vials distributed are Arepanrix®.

ULTRAM® & ULTRACET®: RISK OF SUICIDE AND OVERDOSAGE

In June 2010, the warnings in the prescription information for tramadol was strengthened by the United States Food and Drug Administration (US FDA), to emphasize the risk of suicide for patients who are addiction-prone, taking tranquilizers or antidepressant drugs and to warn of the risk of overdosage.

Risk of suicide:

- Tramadol-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts, as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs.

- Tramadol may be expected to have additive effects when used in conjunction with alcohol, other opioids or illicit drugs that cause central nervous system depression.

Risk of overdosage:

- Serious potential consequences of overdosage with tramadol are central nervous system depression, respiratory depression and death.

Local Scenario

Ultracet® (tramadol hydrochloride/acetaminophen) is the only tramadol-containing combination product registered in Malaysia with Johnson & Johnson Sdn. Bhd. as the product holder. Ultram® is not registered here.

There are 32 oral products with tramadol as single ingredient registered by the DCA.

Since year 2005, the National Centre of ADR Monitoring has received 5 reports associated with respiratory depression with use of tramadol; 4 breath shortness, 1 breathing difficult. No report on suicide attempt or central nervous system depression has been received. Also, there are no tramadol-related deaths.

Johnson & Johnson, has been asked to provide a feedback on this issue.

References:

1. FDA MedWatch. *Ultram (tramadol hydrochloride), Ultracet (tramadol hydrochloride/acetaminophen): Label change*. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm213264.htm [25 May 2010]

LIQUID VITAMIN D SUPPLEMENT PRODUCTS: RISK OF OVERDOSAGE IN INFANTS

Healthcare professionals and consumers should be aware of the potential risk of overdosing infants with liquid vitamin D.

A notification from US FDA states that some liquid vitamin D products come with droppers that hold a greater amount of vitamin D than an infant should receive, which may result in parents or caregivers accidentally giving a harmful amount of vitamin D to their infants.

The American Academy of Paediatrics recommends a dose of 400 IU of vitamin D supplement per day to breast-fed and partially breast-fed infants (first 2 months after birth).

Excessive amounts can cause harmful effects to infants. It may be characterized by nausea and vomiting, loss of appetite, excessive thirst, frequent urination, constipation, abdominal pain, muscle weakness, muscle and joint aches, confusion, fatigue, as well as more serious consequences like kidney damage.

On 17 June 2010, Health Canada has issued an Information Update to alert the public regarding this matter. The regulatory body recommends that all breastfed, healthy term infants aged 12 months and under receive a daily vitamin D supplement of 400 IU, which is the equivalent of 10 micrograms.

Local Scenario

The Drug Control Authority (DCA) has not registered any supplement products with vitamin D as single ingredient. There are 48 products containing vitamin D in combination with other ingredients in Malaysia.

Out of these 48 products, 17 products are indicated for infants. 16 of these products carry a dosage instruction of less than 400 IU vitamin D daily for infants. The recommended daily dose for the remaining product could not be determined as there is a lack of information on the strength of vitamin D. This product, together with another 3 products with the same shortcoming, have been forwarded to Post-Marketing Surveillance Section for further action.

Since year 2000, the National Centre of ADR Monitoring had received 5 reports with the use of supplement products containing vitamin D. All adverse events reported were related to skin disorders (rash, erythema, itching, urticaria) and involved children 1 years of age and above. None of the cases were related to vitamin D overdose. All patients recovered without sequelae.

References:

1. FDA MedWatch. Vitamin D Supplement Products: Medication use error. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm215523.htm. [15 June 2010]

2. MedEffect Canada. Information Update: Proper dosing of liquid vitamin D supplements in infants. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2010/2010_107-eng.php. [17 June 2010]