APRIL 2011

MADRAC

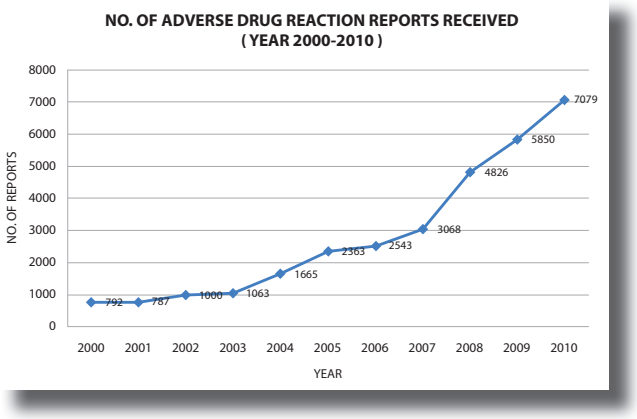
Malaysian Adverse Drug Reactions Newsletter
National Pharmaceutical Control Bureau, Ministry of Health Malaysia
This newsletter is also available on our website: http://www.bpfk.gov.my

ACTIVITIES OF MALAYSIAN ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (MADRAC) FOR 2010

ADVERSE DRUG REACTION (ADR) REPORTING FOR 2010: AN OVERVIEW

A total of 7079 reports were received in year 2010 which follows the ascending trend since year 2000. This figure is a 21% increase from year 2009 (Refer to *Chart 1*).

Chart 1



ADR Reporters

Of the 7079 reports received, 5976 reports (84.4%) were sent in by healthcare professionals from the government sector. This is an increase from last year's 4698 reports from the government sector. The year 2010 also showed an increase (72.2%) in the number of ADR reports from private healthcare professionals

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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
Peti Surat 319, Jalan Sultan,
46730 Petaling Jaya,
Selangor.

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

Editorial Staff

(248 reports) compared to 2009 (144 reports). However, reports from Marketing Authorisation Holders (MAH) saw a decreasing trend since year 2008. There was also an increase in the number of reports from the 'Others' category of reporters due to the higher number of reports submitted by nurses (338 reports) in accordance with the HPV national immunisation programme (Refer to *Chart 2*). Only 7 reports were submitted by consumers.

ADR Reports by State

For all reports in year 2010, Selangor state contributed the highest number of ADR reports (1557; 22.0%) followed by Sabah (886; 12.52%) and Perak (845; 11.9%). All other states exhibited an encouraging increase in the number of ADR reports submitted compared to year 2009 except for Johor, Melaka, Penang and Sarawak.

ADR Reports by System Organ Class (SOC)

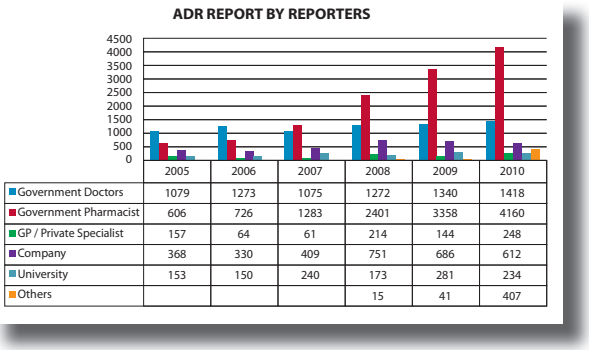
Classification of all reports according to SOC indicated that most adverse events reported were of the '*Skin and Appendages Disorders*' SOC (20.2%) followed by '*Body as a Whole – General Disorders*' SOC (16.7%) and '*Central and Peripheral Nervous System Disorder*' SOC (15.4%). (Refer to *Chart 3*)

The reports involved 7753 suspected products, of which 7134 (92.0%) were prescription products while 443 (5.7%) were non-prescription products. The remaining 176 products (2.3%) involved were traditional products, cosmetic products, food products and unregistered products.

ADR Reports by Pharmacological Groups

Out of 5569 reports involving prescription products (excluding vaccines), more than half (56.9%) reported suspected drugs from the following 3 pharmacological groups i.e. *Cardiovascular* (26.1%), *Anti-infective* (21.0%) and *Analgesic* (9.8%) (Refer to *Chart 4*). This follows the trend in year 2009 where the top 3 major pharmacological groups were also *Cardiovascular*, *Anti-infective* and *Analgesic.*

Chart 2



	2005	2006	2007	2008	2009	2010
Government Doctors	1079	1273	1075	1272	1340	1418
Government Pharmacist	606	726	1283	2401	3358	4160
GP / Private Specialist	157	64	61	214	144	248
Company	368	330	409	751	686	612
University	153	150	240	173	281	234
Others				15	41	407

Chart 3

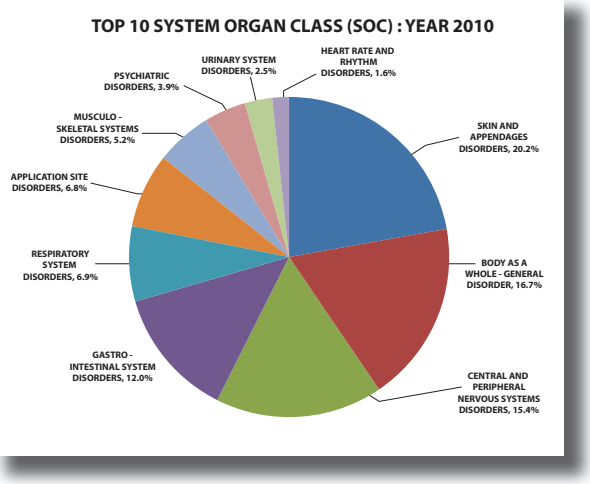
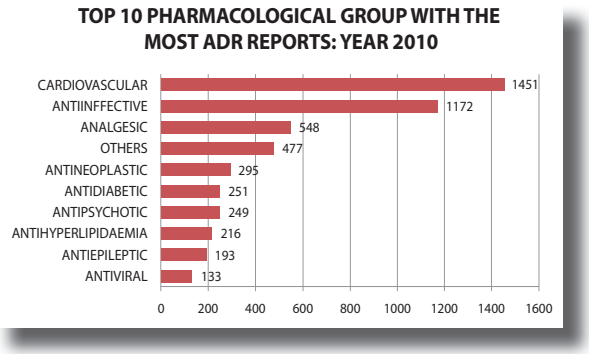


Chart 4



Vaccine ADR Reports

In year 2010, there was a surge in reports for vaccines (1565 reports) compared to the figure in 2009 (242 reports). This is due to the launching of the national Human Papillomavirus (HPV) immunisation programme as well as the usage of H1N1 vaccines in lieu of the H1N1 pandemic.

ADVERSE EVENTS FOLLOWING IMMUNISATION (AEFI) REPORTS FOR HUMAN PAPILLOMAVIRUS (HPV) VACCINE

Introduction

Ministry of Health (MOH) Malaysia had issued a circular (KPK Bil 12/2010 Bil (18) KKM.171/BKP/06/29/0422) Jld 3) dated 26 April 2010 regarding the HPV national immunisation programme launched for 13 year old teenage girls. This programme is a part of the National Children Immunisation Programme (*Program Pelalian Kanak-Kanak Kebangsaan*). The immunisation will only be given to those with written consent from their parents or guardian.

As optimum protection from the risk of cervical cancer can only be produced with 3 complete doses, the HPV vaccine needs to be given according to the following schedule:

i) First dose on any calendar date
ii) Second dose to be given 1 month after the first dose
iii) Third dose to be given 6 months after the first dose

The use of HPV vaccine is contraindicated in:

i) Patients who experienced serious adverse reactions after receiving the previous HPV vaccine dose
ii) Patients who are allergic to yeast (For the quadrivalent HPV)
iii) Patients who are allergic to latex (For the bivalent HPV)

Any adverse events due to the HPV vaccine must be reported to the National Pharmaceutical Control Bureau (NPCB) according to the guidelines laid out in the Malaysian Vaccines Safety Pharmacovigilance Guidelines (*Garispanduan Farmakovigilans Keselamatan Vaksin*). To facilitate reporting of adverse events by the teenagers or their guardians, a simplified form for mild AEFI has been prepared (*Borang Pemantauan Kesan Sampingan Ringan Selepas Pelalian*) by NPCB in collaboration with the Disease Control Division (*Bahagian Kawalan Penyakit*). This form is distributed by the health personnel to every teenager receiving the vaccine. However, in the event of a serious adverse reaction, health personnels are required to complete the usual ADR form as per the aforementioned guidelines.

The HPV vaccine selected by the Malaysian MOH for this programme is the bivalent HPV vaccine Cervarix® by GlaxoSmithKline Pharmaceutical. Cervarix® contains the recombinant L1 protein from HPV strains type 16 and 18. In Malaysia, the only other HPV vaccine registered apart from Cervarix® is Gardasil® from Merck Sharpe & Dohme (I.A) Corp. which is a quadrivalent HPV vaccine containing recombinant L1 proteins type 6, 11, 16 and 18.

Adverse Events Following Immunisation of HPV

The adverse events reporting system used in Malaysia is a 'spontaneous' reporting system. However, for the national HPV vaccination programme, adverse event reporting by the patient is 'cohort' based as each teenage girl receiving the vaccine will be given the simplified form (as mentioned above) for them to report any adverse events experienced subsequent to the immunisation.

The NPCB National Centre of ADR Monitoring has received AEFI reports on both HPV vaccines registered in Malaysia (Gardasil® and Cervarix®):

a) Up until 31 December 2010, 412 AEFI reports concerning HPV vaccines (0.16% of the total doses given for the HPV national immunisation programme) have been received contributing to a total of 736 adverse events where 3 reports concerned Gardasil®. Majority of the adverse events reported (29.8%) were in the '*Central & Peripheral Nervous System Disorder*' SOC, followed by the '*Application Site Disorders*' SOC (27.0%) and the '*Gastro-Intestinal System Disorder*' SOC (17.5%).

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b) The 10 most commonly reported adverse events are as shown below:

NO	EVENT	FREQUENCY	PERCENTAGE (%)
1	HEADACHE	161	21.88
2	INJECTION SITE PAIN	113	15.35
3	NAUSEA	77	10.46
4	INJECTION SITE SWELLING	53	7.20
5	VOMITING	45	6.11
6	WEAKNESS GENERALISED	32	4.35
7	FEVER	31	4.21
8	GIDDINESS	24	3.26
9	LIMB WEAKNESS	22	2.99
10	DIZZINESS	21	2.85

There were no reports of allergic reaction.

c) 51% of the AEFI reported occurred less than 30 minutes after administration of the injection.

d) The incidence for the adverse events reported are lower than the incidence rates documented in the Cervarix® package insert (PI) except for nausea and vomiting which reported a higher prevalence. However, this is not a pronounced increase.

e) According to the World Health Organization (WHO) guidelines, an adverse event is classified as serious if the reaction:
- Results in death
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is life-threatening
- Is a congenital anomaly/birth defect

The NPCB has received 3 serious reports with the events *Fits Not Otherwise Specified (NOS), feeling cold, spasms* and *adenocarcinoma* relating to HPV vaccine. However, investigations conducted on all 3 reports did not show a causal relationship between the event and the vaccine.

Conclusion

The trend and types of adverse events reported are common symptoms experienced with immunisation. Although there were serious cases reported, there is no evidence for a safety concern nor was there any issue relating to the quality of the vaccine.

Therefore, the benefit-risk balance for HPV vaccines remains positive and NPCB will continue to monitor the AEFI of HPV vaccines particularly for vaccinations through the HPV national programme in line with WHO requirements.

SUMMARY OF MALAYSIAN ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (MADRAC) RECOMMENDATIONS FOR REGULATORY ACTIONS BY THE DRUG CONTROL AUTHORITY (DCA): YEAR 2010

During the course of the year, the following recommendations were proposed by the MADRAC and accepted by the DCA:

No.	MADRAC Meeting	Products Involved	Recommendations	DCA Meeting
1	114 (1/4/10)	Sibutramine	**Additional Warnings on Increased Cardiovascular Risk** • A summary description of the results of the SCOUT (Sibutramine Cardiovascular Outcome Trial) study	224 (28/1/10)
2	114 (1/4/10)	Red yeast rice (monascus purpureus)	**Additional Warnings on Effects of Naturally occurring Lovastatin in Products containing Red Yeast Rice:** • *"This product contains naturally occurring lovastatin. Do not take this product if you are already on statin products (Lovastatin, Atorvastatin, Fluvastatin, Pravastatin, Simvastatin etc).* *Concurrent use of fibrates may cause severe myositis and myoglubinuria.* *Please consult your physician/pharmacist before using this product."*	227 (29/4/10)
3	115 (20/5/10)	Propylthiouracil	**Boxed Warning on Severe Liver Injury and Acute Liver Failure:** *Severe liver injury and acute liver failure, some of which have been fatal, have been reported in adult and pediatric patients using this medication*	228 (27/5/10)
4	115 (20/5/10)	Carbocysteine, acetylcysteine and methylcarbocysteine (mecysteine)	**Contraindication due to Risk of Aggravation of Respiratory Symptoms** • Contraindicated in children below 2 years of age	228 (27/5/10)

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No.	MADRAC Meeting	Products Involved	Recommendations	DCA Meeting
5	117 (7/10/10)	Rosiglitazone	**Updates to the Indication, Contraindication and Warning and Precaution Sections of the Product Package Insert due to Risk of Congestive Heart Failure.** • Use of rosiglitazone was contraindicated in patients with established NYHA Class I to IV heart failure or history of cardiac failure, patients with known ischaemic heart disease, and patients with Acute Coronary Syndrome (unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI)). • Rosiglitazone is to be prescribed to new patients only if they are unable to achieve adequate blood glucose control with all other oral anti-diabetic medications and it is the only suitable alternative in the healthcare professional's assessment as mono therapy or in combination with other oral anti-diabetic. **Additional Black Boxed Warning** - *Rosiglitazone is contraindicated in patients with established NYHA Class I to IV heart failure and in patients with known ischaemic heart disease, particularly in those taking nitrates.* - *Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. Patients on rosiglitazone should be monitored carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnoea, and/or oedema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone must be considered.*	234 (22/11/10)
6	118 (16/12/10)	Sibutramine	**Cancellation of the Registration of All Sibutramine Products due to Risk of Major Cardiovascular Events** • Any new products containing sibutramine will also not be registered in Malaysia.	235 (23/12/10)

SAFETY ISSUES OF CURRENT INTEREST

MULTAQ® (DRONEDARONE): DRUG-INDUCED HEPATOTOXICITY

In November 2010, the Pharmacovigilance section was alerted by Sanofi-Aventis about cases of rare but severe liver injury, including two cases of acute liver failure leading to hepatic transplantation, following administration with Multaq® (dronedarone hydrochloride). These case reports triggered a comprehensive analysis of all available data on potential hepatic effects of dronedarone by the company and a summary was submitted to NPCB for further review.

Local Scenario

In Malaysia, Multaq® is approved for use in clinically stable adult patients with a history of or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate.

It is contraindicated in patients with unstable haemodynamic conditions including patients with symptoms of heart failure at rest or with minimal exertion (corresponding with NYHA class IV and unstable class III patients) as this patient group has a greater than two-fold increase in risk of death.

Comparison with Amiodarone

Aspects	Dronedarone	Amiodarone
Chemical Properties	Dronedarone is a non-iodinated amiodarone analogue. Amiodarone is a commonly used anti-arrhythmic but is limited by the toxic effects caused by its high iodine content (pulmonary fibrosis, thyroid disease). The removal of the iodine moieties in dronedarone reduces the toxic effect on the thyroid and thus does not cause iodine-related adverse reactions. Dronedarone is also less lipophilic due to the addition of a methylsulfonamide group which reduces its neurotoxic effects, has a much smaller volume of distribution and a significantly shorter elimination half-life of 24 hours compared to those of amiodarone.	
Pharmaco-kinetics	**Absorption**: • Tmax, oral: 3-6 hours • Bioavailability, oral: 15% with high fat meals • Effect of food: ↑ absorption (2-4 fold) **Distribution**: • Vd: 1400L • Protein binding, albumin: > 98% **Metabolism**: • Liver: extensive, primarily by CYP3A4 • N-debutyl metabolite: active **Excretion**: • Fecal: 84% • Renal: 6% **Elimination half life**: • Dronedarone: 25-30 hours • N-debutyl metabolite: 20-25 hours	**Absorption**: • Tmax, oral: 3-7 hours • Bioavailability, oral: ≈ 50% (35-65) • Effect of food: ↑ absorption (rate and extent), ↓ Tmax by 37%, ↑ Cmax by 3.8 times (2.7-4.4) and ↑ AUC by 2.3 times (1.7-3.6) **Distribution**: • Vd: about 60L/kg • Protein binding, albumin: ≈ 96% **Metabolism**: • Liver: extensive, primarily by CYP3A4 and CYP2C8 • N-desethylamiodarone (DEA): active **Excretion**: • Bile: primary excretion site • Renal: negligible amount (< 1%) • Dialysable: no **Elimination half life**: • Oral, chronic dosing: Amiodarone: 26-107 days DEA: 61 days • IV, single-dose: Amiodarone: 9-36 days DEA: 9-30 days

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Aspects	Dronedarone	Amiodarone
Local Products & Usage	Multaq® is the only product containing dronedarone in Malaysia. This product has been launched scientifically on 19 Feb 2011. As of Jan 2011, 241 boxes of sample have been distributed to selective prescribers in the private hospitals. Exact usage by these prescribers is unknown.	There are 7 registered products containing amiodarone in Malaysia under the tradenames Cardilor® (IDS Services), Amiohexal® (Imeks Pharma), Eurythmic® (Medispec), Aratac® (Merck), Cordarone® and Cordarone Injection® (both Sanofi-Aventis). The first amiodarone-containing product was registered in year 1987.
Literature	There is no documented liver injury in Micromedex.	Amiodarone has been associated with increased liver enzymes in 4% to 9% of patients, but this is usually asymptomatic. There have been reports of hepatic injury, including hepatitis and cirrhosis, which may lead to a fatal outcome. Also, rapidly progressive fatal hepatic failure has occurred one month after starting treatment with amiodarone.
MADRAC Database	No reports have been received.	82 reports have been received since year 2001, of which 29 were associated with hepatic reactions (52 events). There were 30 events of increased hepatic enzymes (57.7%), 8 events of jaundice (15.4%) and 4 events of hepatitis (7.7%).
WHO Database	Reports since year 2010: - hepatitis (acute, toxic, ischaemic) : 9 - hepatocellular injury : 6 - jaundice : 3 - hepatic failure : 2	Reports since year 1981: - hepatitis (acute, chronic, fulminant, toxic, ischaemic) : 428 - hepatocellular injury : 102 - jaundice : 131 - hepatic failure : 132

Company's Feedback

Sanofi-Aventis (M) has revised the local Multaq® labelling in accordance with the Company Core Data Sheet in the *Special Warnings and Precautions for Use* and *Undesirable Effects* sections.

The company has also issued a Dear Healthcare Professional Communication (DHPC) in March 2011 to ensure that all healthcare professionals are properly made aware of this revision.

Reference:

1. Sanofi-Aventis. Dronedarone: Summary of hepatic safety data. [22 Disember 2010]
2. FDA MedWatch. Multaq® (dronedarone): Drug safety communication – Risk of severe liver injury. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm240110.htm [14 January 2011]
3. EMA. Benefit-risk review of Multaq started. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/01/news_detail_001187.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1 [21 January 2011]

KETOPROFEN-CONTAINING TOPICAL MEDICINAL PRODUCTS: RISK OF PHOTOALLERGY REACTIONS

A communication from Sanofi-Aventis regarding the European Commission's decision to maintain the marketing authorisations for topical medicinal products containing ketoprofen for human use was received by the Pharmacovigilance section in January 2011.

This is the opinion of the Committee of Medicinal Products for Human Use (CHMP) following the decision of the French National Competent Authority (Afssaps) to suspend the marketing authorisations of all ketoprofen-containing topical products in France in December 2009. It was due to the conclusions of a national assessment (2001-2009) showing a stabilised incidence of photoallergy (allergic reactions to a medicine following exposure to sunlight) and the new risk of co-sensitisation with octocrylene, a chemical sun filter belonging to the cinnamate family included in several cosmetic and hygiene products. These reactions occurred even without exposure to sunlight.

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) widely used in the treatment of minor pathologies such as arthritis deformans (rheumatoid arthritis), periarthritis humelo-scapularis (frozen, painful or stiff shoulder), peritendinitis or tendonitis, muscular pain, as well as pain and swelling resulted from trauma (contusion, distorsion etc).

In Malaysia, the topical formulations available are gel and plasters. After topical applications, ketoprofen is absorbed slowly through the skin and does not significantly accumulate in the body.

Data Summary

Following a thorough review of all available data, the CHMP concluded that:

- under normal conditions of use, topical ketoprofen is associated with the risk of photosensitivity, including photoallergy reactions which can be serious;
- there is a rare incidence of co-sensitisation with octocrylene;
- further risk minimisation measures (RMM) are needed aiming to limit the risk of photosensitivity reactions including photoallergy reactions;
- all topical ketoprofen-containing products should include safety information to address the above concerns and therefore amendments to the relevant sections of the Summary of Product Characteristics, Labelling and Package Leaflet were recommended.

In view of these findings, the CHMP concluded that the benefit/risk balance of ketoprofen containing medicinal products remains favourable under the normal conditions of use.

Local Scenario

There are 8 ketoprofen-containing topical products registered in Malaysia, of which 5 are in gel form (Deprofen®, Fastum®, Kenofen®, Ketofen®, Orudis®) and the remaining 3 are plasters (Kefentech®, Kenhancer®, Ketotop®).

Ketoprofen 2.5% Gel and Ketoprofen 30mg Transdermal Plaster are listed in the MOH Drug Formulary.

All local package inserts for these products warn about hypersensitivity reactions and recommend immediate discontinuation of usage following skin reaction. Only Orudis Gel® has contraindicated its use in patients with a history of any photosensitivity reaction and sun exposure during treatment and 2 weeks after its discontinuation. All but 3 products recommend protecting the treated area by wearing clothing or avoiding sun exposure to minimise the risk of photosensitisation.

Since year 2000, the National Centre of ADR Monitoring has received 3 reports (5 events; contact dermatitis, erythema, face oedema, oedema, oedema periorbital) on topical ketoprofen products. At the time of reporting, 2 patients recovered while the outcome for the third patient was not known.

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.

Reference:

1. Sanofi-Aventis. Ketoprofen-containing topical medicinal products – European Commission decision to maintain the marketing authorisations. [3 January 2011]
2. EMA. European Medicines Agency confirms positive benefit-risk balance of topical formulations of ketoprofen. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2010/09/human_pha_detail_000006.jsp&murl=menus/medicines/medicines.jsp&mid=&jsenabled=true [22 July 2010]

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RELATED PUBLICATIONS

CLINICAL MANIFESTATIONS OF CUTANEOUS ADVERSE DRUG REACTIONS

Since year 2000, the '*Skin & Appendages disorders'* system organ class (SOC) has consistently been the SOC with the most adverse events reported. In 2010, the events in this SOC made up 20.2% (2637 reports) of the total adverse events reported.

However, an accurate description of the skin reactions reported was difficult to obtain as most of the reports did not specify the type of rash nor provide a description of the cutaneous reaction. There were 746 events reported as '*rash*' which is 28.3% of the '*Skin & Appendages disorders*' SOC. Therefore, in an effort to further improve the quality of the reports and facilitate the evaluation of the ADR reports concerning cutaneous reactions, the MADRAC in its 114th Meeting on 1 April 2010, decided to create a list of cutaneous adverse drug reactions to aid reporters in providing a more complete depiction of the cutaneous reaction.

The list (Appendix A), complete with glossary and pictures (Appendix B), was finalised with the help of Datuk Dr. Roshidah Baba (Head of Dermatological Services, Head of Dermatology Department & Senior Consultant Dermatologist, Hospital Melaka) and her team and has been distributed to all states. It is also available in the BPFK website (http://www.bpfk.gov.my) under the "MADRAC (Adverse Drug Reactions)" section.

Reporters are highly encouraged to make full use of this list and submit it (Appendix A) simultaneously with the ADR form when reporting any cutaneous adverse drug reaction.

APPENDIX A

CLINICAL MANIFESTATION OF CUTANEOUS ADVERSE DRUG REACTION

1. Type of cutaneous adverse drug reaction (please √)
   - You are allowed to choose more than one of the following.

1.	Acneiform Eruption		9.	Pruritus only	
2.	Alopecia		10.	Purpura	
3.	Erythema multiforme		11.	Toxic Epidermal Necrolysis	
4.	Erythema nodosum		12.	Stevens-Johnson Syndrome	
5.	Fixed drug eruption		13.	Urticaria / Angioedema	
6.	Maculo-papular rash (exanthema)		14.	Vasculitis	
7.	Photosensitivity		15.	Vesiculobullous reaction	
8.	Pigmentary changes		16.	Others :	

2. Please specify part of the body affected

_____

_____

_____

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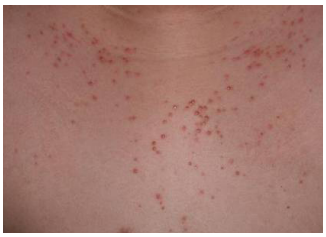
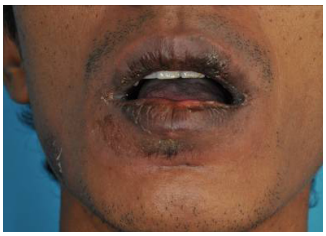
APPENDIX B

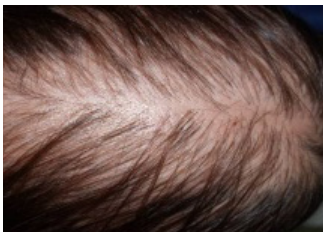
Glossary and Pictures of Clinical Manifestation of Cutaneous Adverse Drug Reaction



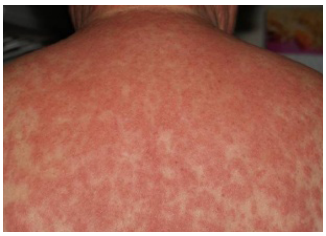
Acneiform Eruption
Rash resembling acne



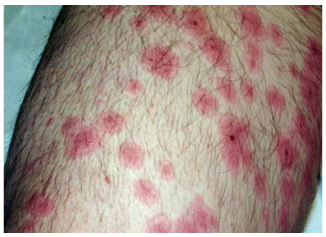
Fixed drug eruption (FDE)
A few, round erythematous patch, blisters or erosions over the lips, face, hands, feet and genitalia. FDE recurs at the same sites and may extend to other areas if the drug is taken again.



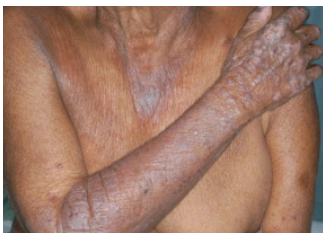
Alopecia
Excessive hair loss



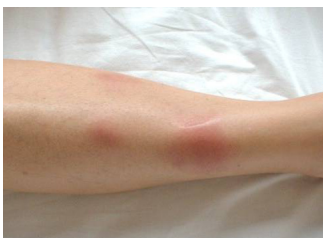
Maculo-papular rash (exanthema)
Generalised small red macules and papules



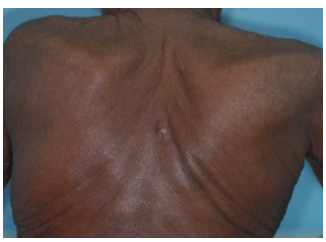
Erythema multiforme
Target lesions comprising of a dark central spot surrounded by a pale halo which is then surrounded by a red ring, occasionally blister at the centre.



Photosensitivity
Erythema or rash over sun exposed areas.

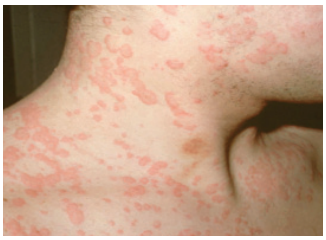


Erythema nodosum
Painful deep red nodules over the legs



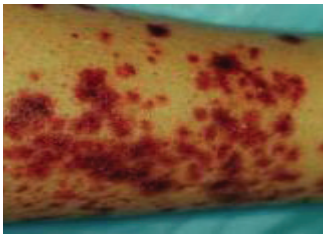
Pigmentary changes
Colour changes of skin, hair, nails and mucous membranes.

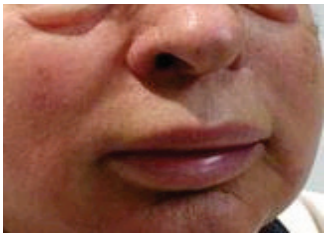
No Specific Image



Pruritus
Itch of the skin without rash

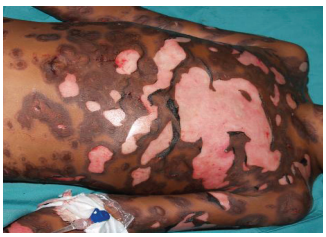
Urticaria
Eruption of wheals/ hives lasting less than 24 hours

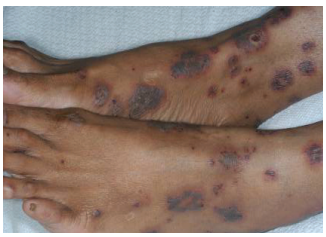




Purpura
Non-blanching, dark red macules or bruises due to bleeding from small blood vessels.

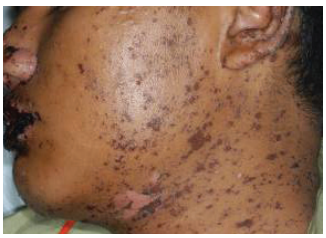
Angioedema
Swelling of the mucous membrane (oral/ eye/ genitalia). May be associated with laryngeal oedema if severe.

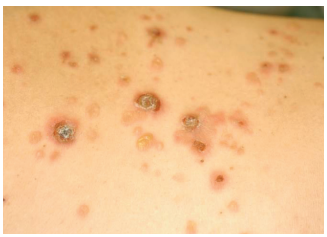




Toxic epidermal necrolysis
Life-threatening variant of Stevens-Johnson Syndrome with large areas of denuded skin

Vasculitis
Palpable purpura





Stevens-Johnson Syndrome
Serious variant of erythema multiforme with involvement of more than 2 mucous membranes (oral/ eye/ genitalia)

Vesiculobullous reaction
Blistering eruption of the skin