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Adverse Drug Reaction (ADR) reports and comments on this bulletin should be sent to:

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The Director,
Drug Control Department
Ministry of Health
PO Box 848, Abu Dhabi
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Fax 02 6313742

Medicines Information Unit e-mail miu@moh.gov.ae

A form for recording ADR reports can be downloaded from the Ministry webpage; URL http://www.moh.gov.ae/moh_site/phar_med/medsaf/d_form.htm
Introduction

There are many excellent medicine information sites available on the Internet and Internet access is becoming a common and essential tool for healthcare workers. With this in mind, we have redesigned the MOH Medicines Information Bulletin. We are especially grateful to the WHO newsletter which we receive. Relevant parts of that newsletter are reproduced in this bulletin.

Our aim is to alert busy pharmacists, doctors and nurses to information that is most relevant to the medicines used in the UAE.

Our bulletin will be available on the MOH web site as well as being distributed as hard copy. We also hope to set up an email distribution. Web versions will include hypertext links to the original source where possible.

All doctors and pharmacists are encouraged to report suspected adverse drug reactions, especially:

- those involving new medicines, or
- those suspected of causing hospital admission, prolonging hospital stay or
- resulting in death or birth defects
- or appearing in this bulletin.

Hospitals should have a system for monitoring these reports but individuals can send their reports to the Director of the Drug Control department who monitors these in collaboration with the WHO medicines safety unit in Uppsala, Sweden.

A form for reporting suspected adverse reactions is available on the internet:
http://www.moh.gov.ae/moh_site/phar_med/moh_p_m.htm

Action taken in the UAE

Pan Pharmaceuticals

Pan Pharmaceuticals is an Australian company that is registered with Ministry of Health as a Manufacturer of General Sale Vitamins and Herbal supplements as well as a Contract manufacturer for other Registered Pharmaceutical Companies.

The UAE Ministry of Health has decided to suspend the Registration of PAN Pharmaceuticals and to cancel the UAE registration of 17 General Sale items manufactured by this company following action taken by the Australian authorities (see list below).

Any of these products manufacture after 1st May 2002 should be returned to the distributor, Al Noor Medical Store, Sharjah.

The 17 products are all dietary supplements and are listed below;

- Bran Super Hi Fiber Enervit
- Evening Primrose Oil 100mg Enervit
- Garlic and Lecithin Enervit
- Ginseng with Bee Pollen Time Release Enervit
- Ginseng with Vitamins
- Ginseng, Bee Pollen, Vitamin E
- Muscle Builder
- Multivitamins & Minerals
- Olive Pearls with Zinc and Vitamin C
- Royal Jelly 1000mg
- Royal Jelly 500mg & Natural Vitamin E 200iu
- Royalvit Co-Enzyme Q10
- Shark Liver Oil
- Stress B with C slow release
- Vitamin A 10,000iu Enervit
- Weight Gain
- Woman Beauty (Hair Skin and Nails)

The ministry is in direct contact with the Australian authorities and is monitoring the situation for further developments.

See the original and ongoing Australian announcements on the internet at URL: http://www.health.gov.au
The following innovative medicines have been granted UAE marketing approval by
the higher drug registration committee in the Ministry of Health (meeting Number
77, January 2003). Several other medicines were given provisional approval and as soon as these are
confirmed they will appear in our bulletin. The following summary information is
adapted from the Martindale and Drugdex databases of the Micromedex system.
They are arranged according to the British National Formulary (and potential
MOH formulary) chapter structure. Colleagues can read more information there about the drug class. The current
edition of the BNF can be viewed on the internet at
http://www.bnf.vhn.net/home.
Prescribers should also read the full prescribing information provided with the
medicine or available from the company.

2. Cardiovascular system

**Trade name: Simdax Infusion**

*Manufacturer:* Abbott laboratories

*Active ingredient:* Levosimendan

*Indication:* congestive heart failure

*Dose:* Titrated according to response

*Mechanism:* inotropic vasodilator

*Side effects:* Hypotension is the predominant complication following intravenous
simendan, and may limit therapy. Other adverse effects include nausea, headache, and
pain at the infusion site.

*Comments:* Clinical experience with this agent is too limited to assess its ultimate role in therapy.

**Trade name: Teveten**

*Manufacturer:* Solvay Pharmaceuticals

*Active ingredient:* Eprosartan

*Indication:* hypertension

*Dose:* Initially, 600 mg daily once daily
in one or two divided doses,
with titration to 800 mg daily

*Mechanism:* AT1-selective non-peptide
angiotensin II receptor
antagonist

*Side effects:* Well tolerated in clinical
tests, treatment
discontinuation rate 3.9% for
eprosartan compared to 6.5% among placebo controls. Dose,
dosage frequency, age,
gender, or race did not affect overall incidence of adverse
effects of eprosartan.

*Contraindication etc:* As for other
angiotensin II receptor
antagonists

*Comments:* Investigation continues for
congestive heart failure; phase
I clinical trials are underway
for treatment of chronic renal
failure.

7. Obstetrics & Gynaecology

**Trade name: Femoston**

*Manufacturer:* Solvay Pharmaceuticals

*Active ingredient:* Estradiol and
Dydrogesterone

*Indication:* HRT combination for use in
women with an intact uterus.

*Dose:* There are a range of products. The Femoston 1/10 contains
1mg estradiol for 14 days
followed by 14 days combined
with 10mg dydrogesterone. Women whose symptoms are
not controlled on this dose can
move to the Femoston 2/10
which contains 2mg estradiol.
For women who are
established on the cyclical
regime above, a daily estradiol
1mg and dydrogetserone 5mg
fixed combination is available,
Femoston 1/5.

*Mechanism:* Hormone replacement

*Side effects, Contraindication &
Comments:* See the
prescribing information plus
the BNF, chapter 7 for a
detailed description of the
revised benefits and safety
profile of hormone
replacement therapy.

The higher committee also gave
conditional approval to several other
innovative medicines. These will be
reported in the next bulletin after the
companies have met the conditions set
by the committee.
**Medicines Safety**

There follows a summary of medicines safety notices issued in UAE and internationally during the previous months. Here we have focussed on those medicines that are used in the UAE. Where available, the number of reports to the WHO is reported. Not all the labelling changes will apply to UAE products but doctors and pharmacists should be aware of these current problems. Most of the advice provided here will be included in UAE package inserts as soon as is practical for the company. They are arranged according to the British National Formulary chapter structure. The current edition of the BNF can be viewed on the internet at [http://www.bnf.vhn.net/home](http://www.bnf.vhn.net/home).

2. **Cardiovascular System**

**Indapamide** (Natrilix, Natrilix SR and Indanorm)

Reports of hyponatraemia - indapamide should be prescribed with caution in the elderly. Sodium levels should be measured promptly if the patient displays any change in conscious or mental state.

**Australia.** Since the release of indapamide in the mid 1980s, the Australian Drug Safety authority (ADRAc) has received 164 reports of hyponatraemia associated with its use, making it the most commonly reported cause of hyponatraemia in the 30-year history of ADRAc. Of the 164 reports of hyponatraemia, 68 reports also described hypokalaemia. Most patients were elderly (88% were aged ≥65 years) and the majority were women (82%). In 75 of 129 cases with a documented serum sodium level, the level was ≤120 mmol/L. In Australia, indapamide is also available in combination with perindopril (Coversyl Plus). Despite the lower dose of indapamide in this product compared with the standard indapamide tablet (1.25 vs. 2.5 mg), there have been 5 reports of hyponatraemia associated with ‘Coversyl Plus’ in the first 5 months of 2002. [Reports in WHO file: Hyponatremia 474]


**UAE.** In the UAE we also have Natrilix SR which contains 1.25mg of indapamide.

3. **Respiratory System**

**Inhaled Corticosteroids**

Risk of dose related adrenal suppression in paediatric population – do not exceed the paediatric dose

**UK.** The Committee on Safety of Medicines (CSM) and the Medicines Control Agency (MCA) remind prescribers of the risks of adrenal suppression in children receiving inhaled corticosteroids. Adrenal suppression is a dose-related class effect of all inhaled corticosteroids and prescribers are strongly advised not to exceed the paediatric licensed dosages.

<table>
<thead>
<tr>
<th>Maximum licensed doses in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone 400 mcg/day (age not stated)</td>
</tr>
<tr>
<td>Fluticasone 400 mcg/day (4-16 years)</td>
</tr>
</tbody>
</table>

They are reminded that, because of its greater potency, fluticasone should normally be used at half the dose of beclomethasone.


**UAE.** Inhaled corticosteroids include fluticasone (Flixotide) as well as a wide range of innovator and generic inhalers containing beclomethasone (e.g. Becotide, Becloforte, Beclolem).

4. **Central Nervous System**

**Ergotamine**

Peripheral ischemia due to interaction with enzyme inhibitors – avoid combination

**USA.** FDA and Novartis have strengthened the labelling, including a new boxed warning and updates to the Contra-indications, Warnings, Pre-cautions and Clinical Pharmacology sections of the prescribing information for ergotamine-caffeine (Cafergot) suppositories. The new information states that ergotamine use is contra-indicated with potent CYP 3A4 inhibitors such as ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin, troleandomycin, ketoconazole anditraconazole. This warning is based on the fact that CYP 3A4 inhibition elevates the serum levels of the ergotamine-caffeine preparations which in turn could lead to serious, life threatening vasospasm with cerebral ischemia and/or ischemia of the extremities.


**UAE.** In the UAE, licensed products containing ergotamine include Migrel tablets (Wellcome) but others are used in some hospitals.

5. **Infections**

**Fluoroquinolones**

Reports of tendon disorders and rupture – older patients and concomitant steroids increase the risk. Involves all quinolones but incidence may vary

**Belgium.** The Belgian authorities have received 161 reports of levofloxacin (Tavanic) - associated tendinopathy, including 68 reports of tendon rupture, since the drug was
marketed in 2000 through to 16 April 2002. The average age of patients with levofloxacin-associated tendonopathy was 69 years and about half were receiving concomitant corticosteroid treatment. The average time between the start of levofloxacin treatment and the development of tendonopathy and tendon rupture was 8.4 and 10 days, respectively, with tendon rupture occurring within 48 hours in some cases. Although data from spontaneous reports are insufficient for risk comparisons, the number of cases of tendon disorders reported in association with levofloxacin to date is much higher than that for ciprofloxacin (22 cases), norfloxacin (8), ofloxacin (63) and pefloxacin (16), all of which have been on the market for > 10 years. The most common indications for which levofloxacin was prescribed in patients who experienced tendon rupture were acute or chronic bronchitis (32%) and chronic obstructive pulmonary disease (28%). The report stresses the importance of advising patients to contact their doctor if tendon pain occurs, and points out that the increased risk associated with age and the presence of simultaneous corticosteroid therapy should be considered.

Reports in WHO file: Tendon disorders 888


Mefloquine

Contraindicated for prophylaxis in patients with major psychiatric disorders but can also cause problems in people without a psychiatric history

USA. FDA and Roche strengthened the Contra-indications, Warnings, Pre-cautions and Adverse Reactions sections of the product label for mefloquine (Lariam), the anti malarial drug to include the following additional information. Mefloquine is contraindicated in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis or schizophrenia or other major psychiatric disorders or with a history of convulsions.

During prophylactic use, if psychiatric symptoms such as acute anxiety, depression, restlessness or confusion occur, these may be considered prodromal to a more serious event. In these cases the drug must be discontinued and an alternative medication should be substituted. Healthcare professionals have been notified for the above additions.


UAE. Trade names in the UAE include Lariam plus the generic Mephaquine

6. Endocrine System

Rosiglitazone (AvANDia), Pioglitazone (Actos, Glustin)

Fluid retention and the risk of heart failure

UAE. Rosiglitazone and pioglitazone have been introduced to the UAE for the management of type 2 diabetes. They offer a valuable treatment option for patients with type 2 diabetes. The package inserts and safety advice of these drugs has undergone extensive changes over the last year. Prescribers should ensure that they receive and review the latest prescribing information for these drugs. This includes important new information about fluid retention and the risk of heart failure in a small number of patients. This has led to Glaxo Smith Kline (GSK) setting a 4mg maximum dose for Avandia in patients who are also using insulin.

In line with the USA safety recommendations the MOH department of drug control has issued circulars to remind doctors that fluid retention can occur with these drugs and that this can increase the risk of heart failure. The risk is greater in patients who combine these medicines with insulin. These drugs should be discontinued if there is any deterioration in cardiac status. These drugs should be avoided in patients with NYHA class 3 or 4 heart failure.

Reference:

9. Nutrition and Blood

Epoetin alfa

Subcutaneous administration and PRCA in dialysis patients

Canada & UK. In June 2002 Janssen Ortho Inc, Canada, issued a letter (WHO Pharmaceuticals News-letter No. 2, 2002) that warned health professionals against the subcutaneous (SC) administration of epoetin alfa (Eprex) in patients with chronic renal
failure (CRF) since it could precipitate pure red cell aplasia (PRCA) in these patients. More recently, in December 2002 the UK Committee on Safety of Medicines issued a warning letter with the following additional information.

- Recommended storage conditions for epoetin alfa (between 2 and 8 degrees Celsius) should be adhered to at all times. This stipulation is considered relevant in light of the apparent association between epoetin alfa, PRCA and unmet storage conditions.
- In other approved indications (e.g. Cancer & HIV) there is no evidence of an increased risk of PRCA and in these conditions epoetin alfa (Eprex) may be administered subcutaneously.


UAE. While Eprex treatment is in the hands of a small number of UAE specialists, the subject has generated a much wider interest and the drug control department has issued two circulars on this subject. Most PRCA reports have been with erythropoetin alfa. It is not known whether PRCA will develop in patients receiving the recently introduced darbepoetin (Aranesp) alone. However, the antibodies produced will neutralise any erythropoetin including darbepoetin and substituting is pointless.

Risk of Counterfeit medicine—especially for biotechnology drugs

USA. The FDA has again detected counterfeit medicines in the US market, this time, Procrit, a form of epoetin alfa. Similar cases have been reported with growth hormone and GCSF. Biotechnology medicines are attractive targets for criminal and fraudulent activity. The unit price is high and the penalties if caught are much less than for dealing in illegal narcotics.

UAE. The UAE imports almost all its medicine and the risk of counterfeit medicine is taken very seriously. To minimize this risk in the UAE, all drug imports require a permit. Before issuing the permit the source and supply chain are checked against the registered details. If the drug is not registered then the exporter must be known to the ministry and the importer must demonstrate a clinical need for the medicine.

Reference: Procrit web-page URL: http://www.procrt.com

10. Musculoskeletal and Joint disease

Aspirin

Do not give to children under 16 years (unless specifically advised)

UK. The Medicines Control Agency in UK has announced that the restrictions on aspirin, excluding its use in children under the age of 12, should now be extended to include children up to 16 years of age. All aspirin products will carry a warning to this effect. The announcement is based on the advice of the Committee on Safety of Medicines (CSM) that the risk of Reye’s syndrome, however small, exists also in children under the age of 16. Although the causes of Reye’s syndrome (a disorder found almost exclusively in children and adolescents) are not clearly understood, aspirin use, in the presence of a fever, has been implicated. Therefore, children of this age group, particularly those with a fever, should be given other analgesics not associated with Reye’s syndrome such as paracetamol and ibuprofen. Aspirin should not be given except on the advice of a doctor.


UAE. There are many aspirin containing products in the UAE, many in the form of combination cold and flu remedies. Pharmacists must be vigilant and should check that they are not intended for use by children.

COX-2 inhibitors

Acute neuro-psychiatric events may be a rare class effect of COX-2 inhibitors

Australia. Acute neuropsychiatric reactions are known to occur with the non-selective NSAIDs, and are mentioned in the product information for these medicines. It appears that they may also be a class effect for the selective COX-2 inhibitors, including celecoxib (Celebrex) and rofecoxib (Vioxx). The Australian authorities has received 142 (5% of total) reports of acute neuropsychiatric reactions associated with celecoxib and 49 (8%) with rofecoxib. These report numbers have been calculated after exclusion of psychiatric events which might have been associated with other events such as a hypersensitivity reaction or hyponatraemia. The most common events with celecoxib are confusion, somnolence and insomnia. As a proportion of the total reports, hallucination has been reported more commonly with rofecoxib than with celecoxib.

In many cases the onset of the reaction was dramatic. The event occurred within 24 hours of the first dose in 36 cases with celecoxib and in 14 cases with rofecoxib. In 12 and 4 cases, respectively, the reaction recurred with re-exposure to the drug. In one report marked restlessness was said to occur an hour and a half after taking celecoxib on three occasions, and in another vivid dreams developed on the nights that celecoxib was taken. Prescribers should consider warning patients of the possibility of an acute neuropsychiatric reaction when celecoxib or rofecoxib are prescribed. Reference: Australian Adverse Drug Reactions Bulletin 21:15, Dec 2002. Available from URL: http://www.health.gov.au
Novel Immuno-modulating agents

Etanercept, infliximab and recombinant IL-1Ra are novel immuno-modulating agents that have given fresh hope to hundreds of rheumatoid sufferers. The risk benefit ratio of these drugs remains acceptable, especially compared with more traditional disease modifying drugs. However, more information is coming available about the long-term safety and it’s safety in combination with other immuno-modulating drugs. The drug is used in the UAE by a small number of specialists but the safety information is provided here for general interest.

Etanercept (Enbrel) with recombinant IL-1Ra (Kineret) increases incidence of serious infections without extra benefit

Canada. Amgen Canada Inc, in consultation with Health Canada is warning health professionals about the increased risk of serious infections in patients treated with a combination of etanercept and recombinant human interleukin-1 receptor antagonist (IL-1Ra, Kineret) than in patients treated with etanercept alone. This warning is based on a recently completed clinical trial in the United States that compared the efficacy and safety of etanercept alone with etanercept plus IL-1Ra (Kineret) in patients with rheumatoid arthritis. The trial demonstrated that:

- Patients receiving concurrent IL-1Ra and etanercept had a higher incidence of serious infections than patients receiving etanercept alone
- The combination had no therapeutic benefit over treatment with etanercept alone
- Amgen Canada Inc, in accordance with Health Canada, will amend the Canadian Prescribing Information to include these observations.

Reference:  

Etanercept (Enbrel) and Infliximab (Remicade) may be associated with lympho-proliferative disorders

USA. The FDA and National Cancer Institute suggests that etanercept and infliximab may be associated with lympho-proliferative disorders. Between November 2001 and September 2002 68 cases of lymphomas, ‘possibly or probably’ associated with these two drugs, were reported to the FDA through the adverse event reporting system. 26 reports were received earlier, between May 1999 and 2000; 18 of these reports involved treatment with etanercept and lymphoma was diagnosed a median of 8 weeks after starting therapy. According to the researchers, while definitive conclusions may not be drawn at this stage, the fact that the latent period was quite similar to that associated with lymphomas that develop with immuno-suppressive therapy for patients who receive organ transplants, further implicates these products. The researchers also found that, in two patients, one treated with etanercept and the other with infliximab, there was regression of their lymphoma once treatment was discontinued. They advise that patients should be monitored for ‘spontaneous remission’ after withdrawal of the agent to see if cytotoxic chemotherapy can be avoided, patients’ clinical conditions permitting.

Reference:  

Valdecoxib (Bextra)  
Serious hypersensitivity reactions and skin reactions. High risk in in patients with sulphonamide allergy.

USA. Pharmacia and Pfizer have updated the Warnings section in the product label for valdecoxib tablets (Bextra) to include hypersensitivity reactions (anaphylactic reactions and angioedema) and skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme as possible adverse reactions with the product. The Contraindications section advises that valdecoxib (Bextra) should not be given to patients who have demonstrated allergic-type reactions to sulphonamides. These updates are based on post-marketing surveillance reports of such reactions occurring with valdecoxib (Bextra) in patients with or without a history of allergic-type reactions to sulphonamides. In the US, valdecoxib (Bextra) is indicated for the relief of signs and symptoms of osteoarthritis and adult rheumatoid arthritis, and for the treatment of primary dysmenorrhea.

Reference:  
Reports in WHO file: Face oedema 1, oedema peripheral 1

Valdecoxib (Bextra)  
Serious hypersensitivity reactions and skin reactions. High risk in in patients with sulphonamide allergy.

Europe. The European Medicines Evaluation Agency (EMEA) issued a public statement on parecoxib concerning the risk of serious hypersensitivity and skin reactions. Parecoxib is indicated in the short-term treatment of post-operative pain. Serious reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and

Reference:  
Pharmacia and Pfizer have updated the Medicines Information Bulletin No. 1 2003

Parecoxib (Dynastat)  
Parecoxib is a pro-drug of Valdecoxib and is marketed as an injection in the UAE by Pfizer. It is indicated for post-operative pain control.

Serious hypersensitivity reactions and skin reactions. High risk in in patients with sulphonamide allergy.

Reference:  
exfoliative dermatitis as well as anaphylaxis angioedema have occurred with valdecoxib and these reactions could also occur with parecoxib, the prodrug of valdecoxib. Some of the reactions have occurred in patients with a history of allergic type reactions to sulfonamides. The statement reflects the following: Physicians should note that parecoxib is contra-indicated in patients with a history of hypersensitivity to sulfonamides. Patients with known allergic reactions to sulfonamides may be prone to, and should be aware of, severe side effects with parecoxib. Relevant changes to the prescribing and patient information for parecoxib are posted on the EMEA website.


13. Skin

Isotretinoin (Roaccutane)

Updated information on drug interactions, mood effects and adverse effects in children

USA. Roche has issued a letter to US health professionals advising of several recent changes to the labelling of isotretinoin (known as Roaccutane in the UAE) in the US. Prescribers are advised to exercise caution when prescribing isotretinoin to patients receiving systemic corticosteroids or phenytoin as these could possibly increase the chance of bone toxicity. Aggressive and/or violent behaviours have been added to the USA list of events that may be caused by isotretinoin. Information specific to the paediatric population has been added advising prescribers to use caution when prescribing isotretinoin to patients with a genetic predisposition for age-related osteoporosis or a history of childhood osteoporosis conditions, osteomalacia or other disorders of bone metabolism. It is noted that, in studies of paediatric patients treated with isotretinoin, 29% of patients developed back pain and 22% experienced arthralgias. A statement regarding long-term use has also been added advising that isotretinoin be given at the recommended doses for no longer than the recommended duration.


New help to avoid the chance of prescribing Isotretinoin during pregnancy

Middle East. Isotretinoin is highly toxic to the foetus resulting in severe birth defects. Roche have finalised their guidance on this subject for the Middle East. The leaflet is available in Arabic and English and will be distributed in the near future. The Arabic document and other information will be available on the health professionals section of the new Roche Middle East website; www.roche-arabia.com

This is a rare, but very serious and totally avoidable adverse reaction. Any birth defects which may be linked to the taking of medicines should be reported to the department of drug control and or the drug company.

The World Health Organisation database has 691 reports of foetal disorders associated with isotretinoin, including 35 of multiple malformations.


Drug Interactions

Grapefruit

Avoid grapefruit juice when taking specific drug

Australia. The Australian authorities have received 14 reports, as on December 2002 describing possible drug interactions with grapefruit juice. Grapefruit juice can interact with certain drug substances, affecting their metabolism, leading to higher plasma concentrations of these drugs with serious and even life threatening consequences. Most of the reports involve interactions with dihydropyridine calcium channel antagonists (5 reports) and HMG-CoA reductase inhibitors (statins, 5 reports). Prescribers are reminded that several drug classes may interact with grapefruit juice and that patients receiving these drugs should be made aware of this possibility. Although there are no case reports of significant clinical problems occurring when grapefruit juice and medication ingestion have been separated by more than a few hours, studies suggest that there is a potential for grapefruit juice to interact for up to 3 days after ingestion, particularly with daily consumption. It is therefore recommended that grapefruit juice should be avoided when taking interacting drugs.