DECEMBER 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

REGULATORY MATTERS

ERYTHROPOIESIS-STIMULATING AGENTS (ESA) IN CHRONIC KIDNEY DISEASE: MODIFIED DOSING RECOMMENDATIONS

The results from 3 randomised controlled trials (NHS, CHOIR and TREAT [ref. 3-5]) showed that using ESAs to target a haemoglobin (Hb) level of **greater than 11 g/dL** in patient population with chronic kidney disease (CKD) provides **no additional benefit** than lower target levels, and **increases the risks** for death and serious cardiovascular reactions, such as stroke, heart attack and thrombosis.

To date, no trial has identified a Hb target level, ESA dose, or dosing strategy that does not increase these risks.

Based on these trials, US Food and Drug Administration (US FDA) had recommended a class labeling update on all ESA containing products.

US FDA recommended that ESA should only be initiated when the Hb level is less than 10g/dl inpatients with CKD associated anemia. However, treatment should be discontinued in patients not on dialysis when the Hb level exceeds 10g/dL while in patients who are on dialysis, ESA should be reduced or stopped when the level exceeds 11g/dL.

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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

The European Medicines Agency (EMA) on the other hand has assessed the results of TREAT study and the current recommendation for patients with with CKD is that the maintenance Hb should not exceed the upper limit of the target Hb level (10-12g/dL)

Product Status in Malaysia

Drugs in the class of ESA darbepoetin alfa, epoetin alfa, epoetin beta and methoxy polyethylene glycol-epoetin beta. There are 44 registered products in Malaysia, available under 5 brands (NESP, Eprex, Binocrit, Recormon and Mircera)

Epoetin alfa, epoetin beta and methoxy polyethylene glycol-epoetin beta are listed in the Ministry of Health Drug Formulary, under the category of A* (prescribed only by consultant / specialists for specific indications only).

Currently, the Hb target level recommended in the package inserts for **NESP** and **Mircera** is **11 g/dL**, whereas for **Eprex**, **Binocrit** and **Recormon**, the Hb target level is **10 to 12 g/dL**.

The renal clinical teams in local government hospitals are keeping abreast with the latest news pertaining to ESAs products. The current practice is to target a Hb level of **10-11 g/dL**, down from the target level of 11-12 g/dL previously. Other references used include:

a. MOH clinical practice guidelines (CPG): Management of anaemia in pregnancy and chronic kidney disease – 2007: target Hb level 11-12 g/dL
b. KDOQI guidelines – 2007: target Hb level 10-12 /dL; next revision expected in 2012

Since 2002, the National Centre of ADR Monitoring has received 57 reports on ESAs. None of these reports were related to cardiovascular events.

The National Centre of ADR monitoring will continue to monitor cardiovascular-related reactions in CKD patients receiving ESAs while awaiting the release of new information.

Reference:

1. FDA MedWatch. Erythropoiesis-Stimulating Agents (ESAs) in Chronic Kidney Disease: Drug safety communication – Modified dosing recommendations. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm260641.htm [24> June 2011]
2. EMA. European Medicines Agency 2011 Priorities for Drug Safety Research: Epoetins and tumour progression, shortened survival, mortality and thromboembolic events. <http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/07/WC500094266.pdf [1> July 2010]
3. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin (NHS). N Engl J Med. Aug 1998; 339(9): 584-90.
4. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease (CHOIR). N Engl J Med. Nov 2006; 355(20): 2085-98.
5. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease (TREAT). N Engl J Med. Nov 2009; 361(21): 2019-32.

MULTAQ® (DRONEDARONE): INCREASED RISK OF SERIOUS CARDIOVASCULAR EVENTS IN PERMANENT AF PATIENTS

A clinical study of the antiarrythmic drug, Multaq® (dronedarone) was **discontinued** prematurely due to an excess of **serious cardiovascular (CV) events** in patients receiving dronedarone. The **PALLAS study** is an indication-seeking trial conducted to assess the potential clinical benefit of Multaq® in high risk patients with **permanent** atrial fibrillation (AF).

In Malaysia, Multaq® is indicated in adult clinically stable patients with a history of, or current **non-permanent** AF to prevent recurrence of AF or to lower ventricular rate.

Summary of the PALLAS Study

Reference	Permanent Atrial fibrillation outcome Study using Dronedarone on top of standard therapy (PALLAS) trial (Protocol EFC11405)
Objectives	To assess the clinical benefit of dronedarone 400mg bd on top of standard therapy in patients with permanent AF and additional risk factors.
Design	Multinational, randomised, double-blind, placebo-controlled, parallel-group, multicentre Phase IIIb trial
Participants	First patient was randomised on 19 July 2010. As of 30 June 2011, 3149 patients out of the 10800 planned have been enrolled.
Inclusion criteria	Permanent AF (defined by the presence of AF/atrial flutter (AFL) for at least 6 months prior to randomisation without plans to restore sinus rhythm) AND above 65 years of age with at least one additional CV risk criterion OR the combination of age above 75 years, hypertension and diabetes mellitus
Exclusion criteria	NYHA Class IV heart failure Unstable NYHA Class III heart failure
Primary endpoints	Major CV events (stroke, systemic arterial embolism, myocardial infarction or CV death) CV hospitalisation or death from any cause
Preliminary findings	A significant excess of CV events in the Multaq® group for both primary endpoints, in particular: CV hospitalisation (hazard ratio 1.43; 95% CI 1.07-1.92) stroke (hazard ratio 2.44; 95% CI 1.01-5.87) heart failure events (hazard ratio 2.53; 95% CI 1.68-3.82)
Outcome	The independent Data Monitoring Committee (DMC) recommended discontinuation of PALLAS study. Conclusion has not been drawn as to whether these results are applicable to the current approved population (patients with paroxysmal or persistent AF).

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Product Status in Malaysia

Multaq® 400mg Film Coated Tablet (MAL20102016A) is the only product containing dronedarone in Malaysia and it is not listed in the Ministry of Health Drug Formulary.

The local package insert (PI) has addressed the CV risk associated with the use of Multaq®

Since registration in 2010, the National Centre for ADR Monitoring has received 4 reports (5 events) regarding dronedarone. All are non CV-related.

Recommendations for healthcare professionals:

- Treatment with Multaq® should be restricted to patients with paroxysmal or persistent AF when sinus rhythm has been obtained.
- Treatment with Multaq® should only be started and monitored by a specialist after other antiarrythmic medicines have been considered.
- Multaq® must not be used in patients with permanent AF, heart failure or left ventricular systolic dysfunction.
- Prescribers should consider discontinuation of treatment if AF recurs.
- Multaq® must not be used in patients who have had previous liver or lung injury following treatment with amiodarone, another antiarrhythmic medicine.
- Patients using Multaq® should have their lung function, liver function and their heart rhythm regularly monitored. It is suggested that liver function test and kidney function frequently monitored especially in the first few weeks of treatment.

Reference:

1. FDA MedWatch. Multaq (dronedarone): Drug Safety Communication – Increased Risk of Death or Serious Cardiovascular Events. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm264204.htm [21> July 2011]
2. EMA. European Medicines Agency recommends restricting use of Multaq. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/09/WC500112800.pdf HYPERLINK "http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/07/WC500109180.pdf [22" [22 Sept 2011]
3. Health Canada MedEffect. Multaq: Health Canada reviewing heart-related risk. <http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2011/2011_101-eng.php [21> July 2011]

ACLASTA (ZOLEDRONIC ACID): CONTRAINDICATION IN SEVERE RENAL IMPAIRMENT

In April 2011, a postmarketing safety review by the US Food and Drug Administration (FDA) has identified 16 cases of fatal acute renal failure and 9 cases of renal injury requiring dialysis after Reclast (brand name for zoledronic acid in the US) infusion.

The agency concluded that several risk factors identified as promoting **nephrotoxicity** with the use of Reclast should be added to the label to better inform healthcare professionals of the risk of renal failure.

Risk factors for developing renal failure include:

- Underlying moderate to severe renal impairment
- Concurrent use of nephrotoxic or diuretic medications
- Severe dehydration occurring before or after administration
- Advanced age

Product Status in Malaysia

In Malaysia, there are 3 products containing zoledronic acid registered in Malaysia under the brand names Aclasta and Zometa.

This safety concern is only applicable to Aclasta although zoledronic acid, also sold as Zometa, is approved for treatment of cancer-related indications. Renal toxicity is already addressed in the Warnings and Precautions section of the Zometa label as well as in the Reclast label. Dose reductions for Zometa are provided for patients with renal impairment.

Since 2009, the National Centre for ADR Monitoring has received 18 reports related to Aclasta. Three of the reports (16.7%) were on renal adverse events where all three patients were aged above 75 years old and had developed acute renal failure within the first 3 weeks of treatment. There were also 4 reports (22.2%) of fatal outcome after receiving aclasta treatment and patients were all above 75 years old. However, the cause of death due to multiple co-morbid diseases could not be ruled out.

Company Feedback

Novartis is currently updating its Company Core Datasheet for Aclasta and will be submitting the package insert amendments to health authorities worldwide within first quarter of 2012. The most important change is to **elevate the current warning of not to be used in patients with severe renal impairment (CrCl< 35ml/min) to a contraindication**.

Reference:

1. FDA MedWatch. Reclast (zoledronic acid): Drug safety communication – New contraindication and updated warning on kidney impairment for Reclast. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm270464.htm [1> September 2011]
2. Novartis. Reclast US PI amended to contraindicate patients with creatinine clearance < 35ml/min and issue by FDA a drug safety alert for Reclast (named Aclasta in other countries). [12 September 2011]

PRADAXA (DABIGATRAN ETEXILATE): SAFETY UPDATES ON RISK OF FATAL BLEEDING

Dabigatran Etexilate (Pradaxa) is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran Etexilate also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

In Malaysia, it is approved for the following indications:

- Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery, or total knee replacement surgery,
- Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF).

With its rapid onset, and no need for therapeutic monitoring, dabigatran etexilateis marketed as an alternative to warfarin, another anticoagulant that needs frequent international normalized ratio (INR) monitoring.

However, bleeding is a well-documented side effect by dabigatran etexilate. To minimize this bleeding effect, dabigatran etexilate is contraindicated in patients with severe renal impairment (creatinine clearance; <30mL/min). As a precaution, dose reduction is also needed for moderately renal impaired patients and patients more than 75 years old. There are also other risk factors associated with bleeding in dabigatran;

- Advanced age
- Prior history of bleeding
- Low body weight
- Concomitant treatment with other antithrombotics (e.g. aspirin or clopidogrel) or other drugs which impact the coagulation system
- Presence of oesophagitis/gastritis/gastroesophageal reflux requiring treatment

The risk of bleeding with Pradaxa has been addressed in the package insert since its initial marketing authorisation.

Actions taken by Other countries:

On 6th November 2011, the EudraVigilance database (European Union Drug Regulating Authorities Pharmacovigilance) had recorded a worldwide total of 256 spontaneous case reports of serious bleeding resulting in death in association with the use of dabigatran etexilate

On a separate occasion, as of 31st October 2011, the product holder (Boehringer Ingelheim) had received 340 individual safety reports (ISRs) of serious bleeding in patients who died on treatment with Pradaxa or after it was discontinued. Due to that, the product holder has released a Direct Healthcare Professional Communication (DHCP) to all health care providers on the risk of dabigatran etexilate, and the need to assess renal function before starting the patients on this drug. Dabigatran etexilate's package insert was also revised.

Other regulatory agencies such as European Medicines Agency (EMA) and Therapeutic Goods Administration (TGA) have also revised this new prescribing advice in their package insert respectively.

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Product Status In Malaysia

Since its registration in year 2008, the National Centre for Adverse Drug Monitoring has received a total of 38 reports pertaining dabigatran etexilate, out of which 20 events were related to bleeding and none leading to death.

In these reports, 25% of patients receiving dabigatran etexilate were geriatric patients, while others were of unknown age. Out of these, 2 had a risk factor of bleeding; including concomitant medications and previous history of bleeding, and gastrointestinal (GI) problem while the others were not reported.

The ranges of dose used were from 110mg to 600mg and most of the patients reported had the risk factors associated with bleeding in dabigatran as mentioned above. Therefore it is important that healthcare professionals are aware of the risks of bleeding in patients on dabigatran etexilate therapy.

Health Care Professionals are advised to:

- Not start dabigatran etexilate in patients with severe renal impairment (creatinine clearance <30 mL/min)
- Assess renal function:
  - in all patients before starting dabigatran
  - when a decline in renal function is suspected during treatment (eg, hypovolaemia, dehydration, or with some co-medications)
  - at least annually in patients older than 75 years
  - at least annually in patients with renal impairment
- Check for signs of bleeding or anaemia and stop treatment if severe bleeding occurs
- If a patient needs to be converted from dabigatran etexilate to other vitamin K antagonist, the starting time of the vitamin K antagonist should be adjusted according to the patient´s CrCL as follows:

Renal function	Initiation of dabigatran
CrCL ≥ 50 ml/min	start vitamin K antagonist 3 days before discontinuing dabigatran etexilate
CrCL ≥ 30-< 50 ml/min	start vitamin K antagonist 2 days before discontinuing dabigatran etexilate

- If a patient needs to be converted from Vit. K antagonists to Pradaxa, the Vit. K antagonist should be stopped and dabigatran etexilate can be given as soon as the INR is < 2.0.

Healthcare professionals are encouraged to report adverse events related to the use of Pradaxa to the National Centre for ADR Monitoring. The National Centre of ADR monitoring will continue to monitor the safety profile of dabigatran etexilate, in particular bleeding reactions which lead to a fatal outcome.

COMPARISON WITH WARFARIN

Aspects	Dabigatran	Warfarin
Description	Dabigatran etexilate is an oral prodrug that is metabolized by a serum esterase to dabigatran. It is a synthetic, competitive and reversible direct thrombin inhibitor. Inhibition of thrombin disrupts the coagulation cascade and inhibits the formation of clots. Dabigatran etexilate may be used to decrease the risk of venous thromboembolic events in patients who have undergone total hip or knee replacement surgery, or to prevent stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation therapy is indicated.	An anticoagulant that acts by inhibiting the synthesis of vitamin K-dependent coagulation factors. Warfarin is indicated for the prophylaxis and/or treatment of venous thrombosis and its extension, pulmonary embolism, and atrial fibrillation with embolization. It is also used as an adjunct in the prophylaxis of systemic embolism after myocardial infarction. Warfarin is also used as a rodenticide.
Pharmacodynamics	Dabigatran etexilate is an inactive pro-drug that gets converted to dabigatran, the active form, by esterase-catalyzed hydrolysis in the plasma and liver. Dabigatran, the main active principle in plasma, is a rapid-acting competitive and reversible direct inhibitor of thrombin. Thrombin, a serine protease, is responsible for the conversion of fibrinogen to fibrin during the coagulation cascade. Inhibition of thrombin consequently prevents thrombus development. Dabigatran etexilate inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.	Warfarin, a coumarin anticoagulant, is a racemic mixture of two active isomers. It is used in the prevention and treatment of thromboembolic disease including venous thrombosis, thromboembolism, and pulmonary embolism as well as for the prevention of ischemic stroke in patients with atrial fibrillation (AF).

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Pharmacokinetics	**Absorption:** Tmax: 0.5-2 hours Effects of food: Delays time to peak by 2 hours **Distribution:** Vd: 60-70L **Metabolism:** Metabolized by: esterases and microsomal carboxylesterases **Excretion:** Urine: 85% Fecal: 6% **Elimination Half Life:** $T_{1/2}$: 12-17 hours	**Absorption:** Tmax: 0.5-2 hours Effects of food: Delays time to peak by 2 hours **Distribution:** Vd: 0.14 L/kg **Metabolism:** Metabolized by: esterases and microsomal carboxylesterases **Excretion:** Urine Bile **Elimination Half Life:** R-warfarin $t_{1/2}$=37-89 hours S-warfarin $t_{1/2}$=21-43 hours.
Local Products	PRADAXA is the only product containing Dabigatran registered in Malaysia. There are currently 3 strengths available.	There are 5 registered products containing warfarin in Malaysia.
National Centre for ADR Reporting in Malaysia's Database	Since year 2009: Bleeding:19 Fatal:none	Since year 2000 Bleeding:42 Fatal:none
WHO Database	Report since year 2008: Hemorrhage/ bleeding: 461 cases	Report since year 1979: Hemorrhage/ bleeding: 3639 cases

Reference:

1. Boehringer Ingelheim. Direct Healthcare Professional Communication on the importance of assessing renal function in patients treated with Pradaxa (dabigatran etexilate). [25 October 2011]
2. TGA. Safety Advisory. Dabigatran (Pradaxa) & risk of bleeding: New recommendations for monitoring kidney function. HYPERLINK "http://www.tga.gov.au/safety/alerts-medicine-dabigatran-111103.htm%20%5b3"http://www.tga.gov.au/safety/alerts-medicine-dabigatran-111103.htm [3 November 2011]
3. Boehringer Ingelheim. Pradaxa (dabigatran etexilate): Post-marketing cases of fatal haemorrhages from worldwide spontaneous reporting. [15 November 2011]
4. EMA. Press release. European Medicines Agency updates on safety of Pradaxa. HYPERLINK "http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/11/WC500117818.pdf%20%5b18"http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/11/WC500117818.pdf [18 November 2011]
5. US FDA. Safety. Pradaxa (dabigatran etexilate mesylate): Drug safety communication – Safety review of post-market reports of serious bleeding events. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm282820.htm [7 December 2011]
6. Connolly SJ. et al., Dabigatran versus Warfarin in Patients with Atrial Fibrillation. New England Journal 2009; 361.

BISPHOSPHONATES: RISK OF ATYPICAL FRACTURES OF THE THIGH

In October 2010, the U.S. Food and Drug Administration (FDA) updated the public regarding risk of atypical fractures of the thigh, known as subtrochanteric and diaphyseal femur fractures, in patients who take bisphosphonates for osteoporosis.

These fractures are very uncommon and appear to account for less than 1% of all hip and femur fractures overall. Although it is not clear if bisphosphonates are the cause, these unusual femur fractures have been predominantly reported in patients taking bisphosphonates. They may be related to long-term bisphosphonates use.

FDA has recommended that patients should continue to take their medication unless told to stop by their healthcare professionals and healthcare professionals should discontinue potent antiresorptive medications (including bisphosphonates) in patients who have evidence of a femoral shaft fracture.

In Malaysia

Bisphosphonates, including alendronate, clodronate, etidronate, ibandronate, pamidronate, risedronate and zoledronate, are approved by the Drug Control Authority (DCA) for the following indications:

- Treatment and prevention of osteoporosis in postmenopausal women.
- Treatment of osteoporosis in men to prevent fractures.
- Treatment and prevention of glucocorticoid-induced osteoporosis in men and women.
- Treatment of Paget's disease of the bone (osteitisdeformans).
- Treatment of hypercalcaemia due to malignancy.

The bisphosphonates affected by this notice are only those approved to treat osteoporosis. This notice **does not** affect bisphosphonate products that are used to treat Paget's disease or hypercalcaemia due to malignancy.

Bisphosphonate drugs indicated for osteoporosis listed in the Ministry of Health Drug Formulary are as below:

	Product Name	Active Ingredient
1	Fosamax Tablet 70mg	Alendronate
2	Fosamax Plus Tablet	Alendronate
3	Bonviva Film-Coated Tablets 150mg	Ibandronate

There are 35 bisphosphonate products registered in Malaysia, of which 21 products are indicated for the treatment and prevention of osteoporosis.

Up to December 2011, the National Centre for ADR Monitoring had received 139 reports with the use of bisphosphonates in osteoporosis treatment and prevention:

List of bone-related ADR received for bisphosphonate drugs

Malaysia

alendronate: since 2000; ibandronate: since 2008; risedronate: since 2005

	Active Ingredient	Local ADR Report		Adverse Event	No. of Event
		Total	Bone-related		
1.	Alendronate	113	22	Bone pain	6
				Fracture	2
				Fracture femur	3
				Fracture lower limb	3
				Pain	5
				Skeletal pain	4
2.	Etidronate	0	0	-	-
3.	Ibandronate	6	1	Bone pain	1
4.	Risedronate	10	1	Bone pain	1
5.	Zoledronate	10	0	-	-
	Total	**139**	**24**		

World Health Organization (WHO)

alendronate: since 1995; etidronate: since 1982; ibandronate: since 1999; risedronate: since 1991; zoledronate: since 2002

	Active Ingredient	No. of Event			
		Bone disorder	Bone pain	Osteoporotic fracture	Pathological fracture
1.	Alendronate	306	548	3	108
2.	Etidronate	8	24	0	20
3.	Ibandronate	59	512	3	12
4.	Risedronate	50	251	1	27
5.	Zoledronate	1242	617	2	68

Outcome

Through a series of discussions and consultations with key opinion leaders, MADRAC has proposed additional recommendations in the drug for the clinical practice of bisphosphonates to the Pharmaceutical Services Division. The Ministry of Health's Medicine List Review Panel Meeting approved the inclusion of these recommendations in the drug formulary at its 3rd meeting of 2011 as follows:

Review treatment after 2 years and if there is positive response, treatment may be continued up to 5 years and then re-evaluated. *Treatment should be stopped if there is no positive response after 5 years. Otherwise patients need to be given a drug holiday for 1 to 2 years and then continue treatment if the benefit outweighs the risk.*

The National Centre for ADR monitoring will continue to monitor the safety profile of bisphosphonate-containing products. Healthcare providers are encouraged to report any adverse drug reaction suspected in patients using bisphosphonates in particular ADR related to fractures.

Reference:

1. FDA MedWatch. Bisphosphonates (Osteoporosis Drugs): Label change – Atypical fractures update. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm229244.htm [>13 October 2010]
2. Health Canada. Information Update: safety review of bisphosphonate drugs and the possible risk of rare but serious thigh bone fractures. HYPERLINK "http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2010/2010_175-eng.php[14" http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2010/2010_175-eng.php [14 October 2010]
3. MHRA. Drug Safety Update Volume 2, Issue 8: Bisphosphonates – Atypical stress fractures. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON088118 [March 2009]