WHO PHARMACEUTICALS NEWSLETTER

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

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This Newsletter is also available on our Internet website: http://www.who.int/medicines

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As usual, the WHO Pharmaceuticals Newsletter provides you with the latest safety reports, advice, warnings and other updates from regulatory authorities across the world.

In this edition of the WHO Pharmaceuticals Newsletter readers will also find reports of two important meetings that have recently taken place.

The twenty-second meeting of the Global Advisory Committee on Vaccine Safety (GACVS) was held in Geneva in June 2010. Discussions of the main topics at the meeting are summarised in a feature article on page 18.

WHO Consultants Network for Pharmacovigilance in Africa held its 4th meeting in Lomé, Togo, from 6 to 10 September 2010. The report shows the great and important developments in pharmacovigilance taking place in the African region right now.

A short account of complaints reported to WHO prequalified medicines during 2007-2009 is also included.

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Bevacizumab

Association with hypersensitivity and infusion reactions

Canada. Health Canada and Hoffmann-La Roche Limited have warned that hypersensitivity reactions and infusion reactions have been identified as risks in patients treated with bevacizumab (Avastin®). Bevacizumab is a recombinant humanized monoclonal antibody against the vascular endothelial growth factor, and used to treat certain types of cancer. Health-care professionals are notified that a risk of developing serious hypersensitivity reactions, including anaphylactic and anaphylactoid reactions, has been reported in up to 5% of patients receiving bevacizumab in clinical trials. Post-marketing reports have also captured cases of serious hypersensitivity and infusion reactions. Health-care professionals are also advised that patients should be closely monitored for signs and symptoms of hypersensitivity or infusion reactions during and following the administration of bevacizumab infusion. If a reaction occurs, the infusion should be interrupted and appropriate medical therapies should be administered. The Canadian Product Monograph has been updated to include this information.

Reference:
Advisories, Warnings and Recalls, Health Canada, 19 August 2010, Prescriber Update Vol. 31 (www.hc-sc.gc.ca).

Calcium gluconate injection

New contraindications due to risk of aluminium exposure

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) notified health-care professionals that calcium gluconate injection packed in small-volume glass containers is now contraindicated for use as repeated or prolonged treatment, including an intravenous infusion, in children younger than 18 years and in patients with renal impairment. The Agency states that aluminium can be leached from glass after contact with calcium gluconate solution, leading to a risk of exposure to aluminium which might have adverse effects on bone mineralisation and neurological development in children and those with renal impairment. To limit aluminium exposure, calcium gluconate injection in small-volume glass containers is also contraindicated in the preparation of total parenteral nutrition solutions. Use of calcium gluconate injection packed in plastic containers is recommended to reduce aluminium burden in vulnerable patients. In the UK, parenteral administration of calcium gluconate is authorized where the pharmacological action of a high calcium ion concentration (e.g. in acute hypocalcaemia) is required.

Reference:
Drug Safety Update, MHRA, Volume 4, Issue 1, August 2010 (www.mhra.gov.uk).

Daptomycin

Risk of eosinophilic pneumonia

USA. The U.S. Food and Drug Administration (US FDA) notified health-care professionals and patients about the potential for developing eosinophilic pneumonia during treatment with daptomycin (Cubicin®). The medicine is an antibacterial indicated to treat serious skin infections and bloodstream infections. The Agency identified six cases of eosinophilic pneumonia reported to the Agency's Adverse Event Reporting System (AERS) between 2004 and 2010 that were most likely associated with daptomycin. One additional case of eosinophilic pneumonia most likely associated with daptomycin was identified in the medical literature. In addition, the Agency identified 36 possible cases of eosinophilic pneumonia associated with the use of daptomycin.

Based on the review, the US FDA states that there appears to be a temporal association between daptomycin administration and the development of eosinophilic pneumonia. Eosinophilic pneumonia may lead to progressive respiratory failure and is potentially fatal if not quickly recognized and appropriately managed. The Agency requested that the manufacturer of the product revise the drug label to include this association.

Health-care professionals are advised to closely monitor patients being treated with daptomycin for signs and symptoms of eosinophilic pneumonia, including new onset or worsening fever,

dyspnoea, difficulty with breathing, and new infiltrates on chest imaging studies. Health-care professionals are also advised to discontinue daptomycin in patients exhibiting signs and symptoms of eosinophilic pneumonia and to consider treating symptoms as clinically indicated.

Reference:
FDA Drug Safety Communication, US FDA, 29 July 2010 (www.fda.gov).

Droperidol Injection USP

Risk of severe arrhythmia

Canada. Health-care professionals have been notified of changes to the Canadian Product Monograph for Droperidol Injection USP, including the following.

- Droperidol Injection USP should only be used for the prevention and treatment of post-operative nausea and vomiting in patients for whom other treatments are ineffective or inappropriate.
- Droperidol Injection USP is no longer indicated for use in anaesthesia for sedation or tranquilization, neuroleptanalgesia, or in the management of acute stages of Meniere's disease.
- Droperidol Injection USP is contraindicated in patients with known or suspected QT prolongation
- A new Boxed Warning highlights the risk of QT prolongation and measures to minimize this risk, including a recommendation for screening ECG and cardiac monitoring.

According to the letter to health-care professionals, cases of QT prolongation and/or torsades de pointes have been reported in patients receiving intravenous droperidol. Some cases have occurred in patients with no known risk factors for QT prolongation even at low doses. Some cases have been fatal.

Reference:
Advisories, Warnings and Recalls, Health Canada, 25 August 2010 (www.hc-sc.gc.ca).

Inflenza virus vaccine

Label change due to risk of fever and febrile seizure

USA. The US FDA updated the prescribing information for the influenza virus vaccine Afluria®, which is one of the approved vaccines for the 2010-2011 influenza season in the United States, to inform health-care professionals that the Afluria vaccine has been associated with an increased incidence of fever and febrile seizure among young children reported in Australia, mainly among those less than five years of age. The Agency says that the available data suggest that the increased rates of fever and febrile seizure are only associated with the southern hemisphere formulation of the manufacturer (CSL Limited)'s vaccine. The investigations into the cause(s) of the febrile seizures seen with Afluria vaccine are ongoing.

(See WHO Pharmaceuticals Newsletters No.4, 2010 for Australia's report on febrile reactions in young children following 2010 seasonal trivalent influenza vaccination.)

Reference:
Safety Information, US FDA, 30 July 2010 (www.fda.gov).

Lamotrigine

Label change due to risk of aseptic meningitis

USA. The US FDA notified the public that lamotrigine (Lamictal®) can cause aseptic meningitis. The medicine is used for seizures in children two years and older, and for bipolar disorder in adults. The *Warnings and Precautions* section of the prescribing information and the Medication Guide will be revised to include information about this risk. The decision is based on the US FDA's review of adverse event reports submitted between December 1994 (when the medicine was approved) and November 2009. A total of 40 cases of aseptic meningitis occurring in paediatric and adult patients taking lamotrigine were identified. In most cases, the patients' symptoms were reported to have resolved after lamotrigine was discontinued. In 15 cases, symptoms returned when patients restarted lamotrigine.

The US FDA advises that symptoms of meningitis may include headache, fever, stiff neck, nausea, vomiting, rash, and sensitivity to light.

Health-care professionals are advised that if meningitis is suspected, patients should also be evaluated for other causes of meningitis and treated as indicated, and that discontinuation of lamotrigine should be considered if no other clear cause of meningitis is identified.

***Reference**:*
FDA Drug Safety Communication, US FDA, 12 August 2010 (www.fda.gov).

Methylnaltrexone bromide

Association with gastrointestinal perforation

Canada. Health-care professionals have been notified that the Canadian Product Monograph for methylnaltrexone bromide (Relistor®) has been revised to include the following information:

Based on post-marketing experience, patients with advanced illness and being treated with methylnaltrexone bromide may be at an increased risk of gastrointestinal (GI) perforation if they have such conditions that may be associated with localized or diffused reduction of structural integrity in the GI wall. These include conditions such as cancer, GI malignancy, GI ulcer, Ogilvie's syndrome, and concomitant medications [e.g. bevacizumab, nonsteroidal anti-inflammatory drugs and steroids]. Perforations have involved varying regions of the GI tract (e.g. stomach, duodenum and colon).

Methylnaltrexone bromide is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care. Health Canada and the company advise that methylnaltrexone bromide should be discontinued if patients develop severe, persistent, and/or worsening abdominal symptoms, as these could be symptoms of GI perforation.

Reference:
Advisories, Warnings and Recalls, Health Canada, 28 July 2010 (www.hc-sc.gc.ca).

Midodrine hydrochloride

US FDA proposes withdrawal

USA. The US FDA proposed to withdraw approval of midodrine hydrochloride, which is used to treat the low blood pressure condition orthostatic hypotension, because companies failed to provide evidence of clinical benefit of midodrine hydrochloride. The medicine was approved in 1996 under the US FDA's accelerated approval regulations for drugs that treat serious or life-threatening diseases. This approval required that the manufacturer verify clinical benefit to patients through post-approval studies. The US FDA advises that patients who currently take this medicine should not stop taking it and should consult their health care professional about other treatment options.

Reference:
FDA News Release, US FDA, 16 August 2010 (www.fda.gov).

Modafinil

Indications restricted

Europe. The European Medicines Agency (EMA) has recommended that modafinil-containing medicines should only be used to treat narcolepsy, and that doctors and patients should no longer use the medicine for the treatment of idiopathic hypersomnia, obstructive sleep apnoea and chronic shift work sleep disorder. Modafinil is used to promote wakefulness. A review by the Agency's Committee for Medicinal Products for Human Use (CHMP) was initiated because of a number of safety concerns, relating to psychiatric disorders, skin and subcutaneous tissue reactions as well as significant off-label use and potential for abuse.

The EMA states that based on the available data, the CHMP concluded that the benefits of modafinil-containing medicines continue to outweigh their risks only in the treatment of narcolepsy. For obstructive sleep apnoea, shift-work sleep disorder and idiopathic hypersomnia, the CHMP found that the risk for development of skin or hypersensitivity reactions and neuropsychiatric disorders outweighed the evidence for clinically important efficacy. Therefore, the Committee recommended that these indications should be withdrawn from the marketing authorizations of these medicines.

In addition, the CHMP noted that the risk of development of serious skin and hypersensitivity adverse reactions appears to be higher in children than in adults, and advised that the product information should carry a recommendation saying that modafinil should not be prescribed to children. The CHMP also identified particular cardiovascular risks with modafinil and recommended that the use of the medicine be contraindicated in patients with uncontrolled moderate to severe hypertension and in patients with cardiac arrhythmias.

(See WHO Pharmaceuticals Newsletters No.1, 2009 and No.2, 2008 for reports on adverse skin and psychiatric reactions in Australia and the UK.)

Reference:
Press release, Questions and answers, EMA, 22 July 2010 (www.ema.europa.eu).

Modified-release oral opioids

Suspension of marketing authorizations recommended for opioids using polymethacrylate-triethylcitrate controlled-release systems

Europe. The EMA announced the results of a review of modified-release oral opioids of the WHO level III scale for the management of pain. These medicines, such as morphine and related medicines oxycodone and hydromorphone, are used to treat intense pain that has not been controlled sufficiently with other medicines. The review was conducted following concerns that their controlled-release systems may be unstable in alcohol and that the active substance may be released too quickly when patients take them together with alcohol. This effect called 'dose dumping' could put patients at risk of exposure to large doses of the opioid, which may lead to serious side effects such as respiratory depression.

Based on the available data, the CHMP found that around half of the controlled-release systems tested showed a slight increase in the amount of active substance they released when placed in an alcohol solution, but that this effect was mild and would only have a minor effect on the release of the active substance. However, for once-daily capsules using a polymethacrylate-triethylcitrate coating to control the release of morphine, there was a significant interaction with alcohol. When these capsules were put into a 20% alcohol solution, 80% of the active substance was released within 15 minutes. The EMA states that almost a full day's dose of morphine would be released all at once if a patient were to take the capsule with large drink of neat strong liquor, such as whisky or vodka. In addition, while the CHMP noted that the current product information already contra-indicates drinking alcohol when using strong opioids, it also noted some studies which show that many patients with severe pain drink alcohol while they are being treated with opioids.

Based on the above, the CHMP concluded that modified-release oral opioids using a polymethacrylate-triethylcitrate controlled-release system are highly sensitive to alcohol and that there is a risk of dose dumping if patients drink alcohol while taking them. Therefore, the Committee recommended that the marketing authorizations for these medicines should be suspended until the manufacturers have reformulated them so that they are more stable in alcohol. For all other medicines in the class, the CHMP concluded that their benefits continue to outweigh their risks, but that the existing warnings on the potential interaction with alcohol, e.g. the increased sedative effects of opioids, should be made consistent across all oral opioid medicines of the WHO level III scale.

Reference:
Press release, Questions and answers, EMA, 23 July 2010 (www.ema.europa.eu).

Octagam (intravenous immunoglobulin)

Suspension of marketing authorizations and market withdrawal due to risk of thromboembolic reaction

Europe (1). The EMA has recommended the suspension of the marketing authorizations for Octagam (human normal immunoglobulin 5% and 10%) and a recall of Octagam currently on the market in Europe. Octagam is an intravenous solution that contains human normal immunoglobulin and is used in patients who are at risk of infection, including people with primary immunodeficiency syndrome, or children born with acquired immune deficiency syndrome (AIDS). It is also used in people with certain immune disorders such as idiopathic thrombocytopenic purpura and in patients who have had a bone marrow transplant.

The Agency's Committee for Medicinal Products for Human Use (CHMP) reviewed Octagam because in September 2010, Germany and Sweden suspended the marketing authorizations of these medicines following an unexpected increase in reports of thromboembolic reactions, including stroke, myocardial infarction and pulmonary embolism in patients receiving the medicine. The EMA states that this increase is thought to be related to problems with the

medicine's manufacturing process. Based on the available information, the CHMP noted that there was clear evidence of a recent increase in thromboembolic events associated with Octagam but that the exact cause of the problems could not be identified with certainty. Because of the safety concerns with Octagam, the CHMP recommended that the marketing authorizations for the medicine should be suspended in the European Union and that Octagam currently on the market should be recalled. The suspension will remain in place until the marketing authorization holder has rectified the problem. The EMA recommends that doctors should stop using Octagam and should switch their patients to the most appropriate alternative treatment.

USA (2). Octapharma USA Inc. and the US FDA notified health-care professionals that on 23 September 2010, the company initiated a voluntary market withdrawal of all lots of Octagam (Immune Globulin Intravenous (human)) 5% Liquid Preparation currently in the US market. Previously, on 20 August 2010, the company initiated a voluntary market withdrawal of selected lots, following an increased number of reported thromboembolic events, some of which were serious. The US FDA states that the company has determined that until a root cause of the reported thromboembolic events can be determined and the problem corrected, the most prudent course of action is to suspend further administration of Octagam.

***References**:*
(1) Press release, Questions and answers, EMA, 24 September 2010 (www.ema.europa.eu).
(2) Safety Information, US FDA, 24 September and 25 August 2010 (www.fda.gov).

Rosiglitazone

Suspension of marketing authorizations recommended in Europe, and new restrictions introduced in the USA, due to cardiovascular risk

Europe (1). The EMA recommended the suspension of the marketing authorizations for the rosiglitazone-containing anti-diabetes medicines (rosiglitazone (Avandia®), rosiglitazone/metformin (Avandamet®) and rosiglitazone/glimepiride (Avaglim®)). Rosiglitazone was authorized as second-line diabetes type-2 treatment to be used when other treatments have either failed or are unsuitable for a patient. When rosiglitazone was first authorised in 2000, the use of rosiglitazone was restricted to a second-line treatment and contra-indicated in patients with heart failure or a history of heart failure. Later, the use of these medicines has been further restricted, with new restrictions on the use of them in patients with ischaemic heart disease.

The CHMP initiated the current review of rosiglitazone in July 2010 following the publication of two studies on the risk of cardiovascular problems with the medicine. The EMA states that overall, the accumulated data support an increased cardiovascular risk of rosiglitazone. In view of the restrictions already in place on the use of rosiglitazone, the Committee could not identify additional measures that would reduce the cardiovascular risk. The Committee therefore concluded that the benefits of rosiglitazone no longer outweigh its risks and recommended the suspension of the marketing authorization of the rosiglitazone-containing medicines. Doctors are advised to stop prescribing rosiglitazone-containing medicines, and to review patients who are currently receiving rosiglitazone to amend their treatment. These medicines will stop being available in Europe within the next few months.

USA (2). The US FDA announced that it will significantly restrict the use of rosiglitazone (Avandia®), which is intended to be used in conjunction with diet and exercise to improve glucose control in patients with Type 2 diabetes mellitus, to patients with Type 2 diabetes who cannot control their diabetes on other medications. These new restrictions are in response to data that suggest an elevated risk of cardiovascular events, such as heart attack and stroke, in patients treated with rosiglitazone.

The US FDA states that it will require that the manufacturer GlaxoSmithKline develop a restricted access programme for rosiglitazone under a risk evaluation and mitigation strategy (REMS). Under the REMS, rosiglitazone will be available to new patients only if they are unable to achieve glucose control on other medications and are unable to take pioglitazone (Actos®), which is the only other medicine of thiazolidinediones. The Agency advises that current users of rosiglitazone

who are benefiting from the medicine will be able to continue using the medication if they choose to do so. Doctors will have to attest to and document their patients' eligibility.

Reports in WHO Global ICSR database, Vigibase:

Rosiglitazone

Number of reports (SOC Cardiovascular disorders, General): 4842

Most reported reactions (number of events):

Cardiomegaly	*190*
Cardiovascular disorders	*468*
Heart disorder	*1508*
Hypertension pulmonary	*132*
Cardiac failure	*3177*
Hypertension	*366*
Hypotension	*94*

(See WHO Pharmaceuticals Newsletters No.1, 2008, No.6, 2007, No.4, 2007 for new warnings due to adverse cardiac events in Europe, Canada, the UK, and the USA.)

Reference:
Advisories, Warnings and Recalls, Health Canada 3 June 2010 (www.hc-sc.gc.ca).

Saquinavir

Risk of QT and PR interval prolongation

UK. The MHRA has warned that saquinavir has a marked effect on QT and PR prolongation and is contraindicated in patients at high risk of cardiac arrhythmias, and in patients using other drugs that may cause QT and/or PR interval prolongation. Health-care professionals are advised that saquinavir should be discontinued if patients develop arrhythmias, QT prolongation or PR prolongation. In addition, the use of other drugs that increase plasma levels of saquinavir, such as potent inhibitors of the cytochrome p450 3A4 enzyme, is not recommended (eg, the protease inhibitor nelfinavir, the antifungal itraconazole and proton pump inhibitors such as omeprazole).

Saquinavir (Invirase®) is a protease inhibitor indicated in combination with ritonavir and other antiretroviral drugs for treatment of HIV infection. According to the Agency, a thorough QT study assessed the effects of therapeutic (1000 mg/100 mg twice daily) and supratherapeutic (1500 mg/100 mg twice daily) doses of saquinavir/ritonavir on QT interval compared with placebo and the active control moxifloxacin. The study showed that the saquinavir/ritonavir groups had a prolonged QT interval, and that risk appeared greater than with moxifloxacin. In addition, cases of syncope or presyncope occurred at a higher than expected rate and were seen more frequently on treatment with saquinavir/ritonavir.

(See WHO Pharmaceuticals Newsletters No.3, 2010 and No.2, 2010 for warnings about QT and PR interval prolongation in Canada and the USA.)

Reference:
Drug Safety Update, MHRA, Volume 4, Issue 1, August 2010 (www.mhra.gov.uk.

Tigecycline

Label change due to an increased risk of death

USA. The US FDA reminded health-care professionals of an increased mortality risk associated with the use of tigecycline (Tygacil®) compared to that of other drugs used to treat a variety of serious infections. Tigecycline is approved for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community acquired pneumonia. Tigecycline is not approved for the treatment of hospital-acquired pneumonia (including ventilator-associated pneumonia) or diabetic foot infection.

The US FDA states that the greatest increase in risk of death with tigecycline was seen in patients with ventilator-associated pneumonia. However, the increased risk was also seen in patients with complicated skin and skin structure infections, complicated intra-abdominal infections and diabetic foot infections. The increased risk was determined based on a pooled analysis of clinical trials.

Health-care professionals are advised that alternatives to tigecycline should be considered in patients with severe infections. The drug label has been revised to include information regarding increased mortality risk of tigecycline.

Reference:
FDA Drug Safety Communication, US FDA, 1 September 2010 (www.fda.gov).

Topical ketoprofen

Benefit-risk balance confirmed positive

Europe. The European Medicines Agency (EMA) announced that following a review of topical formulations of ketoprofen, the Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of topical ketoprofen continue to outweigh its risks, but that further measures should be put in place to minimise the risk of adverse skin reactions.

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID). Topical formulations of ketoprofen are used to treat minor trauma, tendonitis, small-joint osteoarthritis, acute low-back pain and phlebitis. The review of these medicines was initiated because of concerns over the risk of skin photosensitivity reactions, including photoallergy, and a new risk of co-sensitisation with octocrylene (a sunscreen agent).

Based on the available data, it was concluded that the risk of serious photoallergic reactions was very low (1 case per 1 million patients treated). The CHMP also noted that, although alternative topical NSAIDs are available in the EU, ketoprofen is the only topical NSAID authorized for the treatment of acute low-back pain. The CHMP recommended the following risk minimisation measures:

- Topical ketoprofen should no longer be available over the counter but should only be obtained with a prescription from a doctor;
- Strengthened warnings on sun exposure should be included in the product information, as well as information on adverse skin reactions when topical ketoprofen is used together with octocrylene;
- The risks of photoallergy with topical ketoprofen and the way to prevent it should be clearly communicated to health-care professionals and to patients.

The CHMP recommended that doctors should inform patients on how to use topical ketoprofen-containing medicines appropriately to prevent the occurrence of serious skin photosensitivity reactions. Patients are advised to make sure that the treated areas are protected from sunlight during the whole period of ketoprofen treatment and the two weeks after stopping the treatment, and to wash their hands carefully after each application of ketoprofen.

Reference:
Press release, Questions and answers, EMA, 22 July 2010 (www.ema.europa.eu).

Antidepressants

The use of antidepressants in pregnancy

New Zealand. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) advised health-care professionals about the use of antidepressants in pregnancy, following a review by the Medicines Adverse Reactions Committee (MARC) of epidemiological studies investigating the association between selective serotonin reuptake inhibitor (SSRI) or serotonin noradrenaline reuptake inhibitor (SNRI) treatment and congenital anomalies. The MARC concluded that there is a small increased risk of congenital cardiac defects associated with fluoxetine, similar to that seen with paroxetine. The possibility of a class effect for all SSRIs or a similar effect with SNRIs could not be excluded.

In addition to the risk of congenital anomalies, SSRIs and SNRIs have been associated with an increase in risk of pre-term birth, persistent pulmonary hypertension of the newborn (PPHN) and neonatal withdrawal symptoms when the mother is treated until the birth of the baby. Medsafe also states that although there is less information on the use of tricyclic antidepressants (TCA) in pregnancy, a recent epidemiological study indicated that TCAs may also be associated with an increased risk of congenital anomalies, pre-term birth and neonatal withdrawal symptoms. Health-care professionals are advised to be aware of the use of antidepressants in pregnancy and to closely observe neonates

(See WHO Pharmaceuticals Newsletter No.2, 2010 for the UK's advice about a possible small increased risk of congenital cardiac defects in association with fluoxetine in early pregnancy.)

Reference:
Prescriber Update Vol. 31, No.3 September 2010, (www.medsafe.govt.nz).

Carbidopa/levodopa and entacapone

Ongoing safety review on possible increased cardiovascular risk

USA. The US FDA notified health-care professionals that it is evaluating clinical trial data that suggest patients taking carbidopa/levodopa and entacapone (the combination product, Stalevo®) may be at an increased risk for cardiovascular events (heart attack, stroke and cardiovascular death) compared to those taking carbidopa/levodopa (the combination product, Sinemet®). Both medicines are used to treat Parkinson's disease. The Agency says that the addition of entacapone to carbidopa/levodopa has been shown to lead to a greater degree of improvement in some of the symptoms of Parkinson's disease than treatment with carbidopa/levodopa alone. The data being evaluated by the US FDA are from a meta-analysis that combined the cardiovascular-related findings from 15 clinical trials comparing entacapone/carbidopa/levodopa to carbidopa/levodopa alone. According to the Agency, in the meta-analysis, a small increased risk of cardiovascular events was found in the group treated with entacapone/carbidopa/levodopa. The Agency also states that several factors make evaluation of these findings difficult.

At this time, the US FDA's review is ongoing. Health-care professionals are advised to regularly evaluate the cardiovascular status of patients who are taking carbidopa/levodopa and entacapone, especially if they have a history of cardiovascular disease.

Reference:
FDA Drug Safety Communication, US FDA, 20 August 2010 (www.fda.gov).

Dexrazoxane

Increased risk of secondary malignancies

UK. The MHRA warned that a three-fold increased risk of secondary malignancies, particularly acute myeloid leukaemia and myelodysplastic syndrome, in association with the use of dexrazoxane (Cardioxane®) combined with chemotherapy, has been reported from randomised clinical trials in children with Hodgkin's disease and acute lymphoblastic leukaemia.

Dexrazoxane is indicated for the prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin in patients with advanced or metastatic cancer after previous anthracycline-containing treatment. The MHRA advises health-care professionals that data on the efficacy of dexrazoxane as a cardioprotective agent in children is very limited and that the possibility of induction of secondary malignancies should be taken into account when considering treatment with dexrazoxane.

***Reference**:*
Drug Safety Update, MHRA, Volume 4, Issue 2, September 2010 (www.mhra.gov.uk).

Estradiol transdermal spray

Ongoing safety review on unintended exposure of children to topical estrogen

USA. The US FDA notified health-care professionals and patients that it is reviewing reports of adverse events associated with estradiol transdermal spray (Evamist®) in children who may have been unintentionally exposed to the medicine through skin contact with women using this product.

Estradiol transdermal spray is used in women to reduce hot flashes during menopause, and sprayed on the skin on the inside of the forearm between the elbow and the wrist. The Agency says that from July 2007 to June 2010, it has received eight post-marketing cases of unintended exposure of children to estradiol transdermal spray. The children ranged in age from three to five years.

The US FDA warns that children unintentionally exposed to estradiol transdermal spray through skin contact with women may experience premature puberty. Patients are advised to make sure that children are not exposed to this medicine and that children do not come into contact with any skin area where the medicine was applied. It is also advised that women who cannot avoid contact with children should wear a garment with long sleeves to cover the application site.

Reference:
Safety Information, US FDA, 29 July 2010 (www.fda.gov).

H1N1 pandemic vaccines and antiviral

Reports of suspected adverse reactions

Europe. (1) The EMA issued the last pandemic pharmacovigilance update that includes a summary of the adverse drug reactions reported up to 8 August 2010, after the use of centrally authorized pandemic vaccines (Arepanrix®, Celvapan®, Focetria® and Pandemrix®) and the antiviral (oseltamivir (Tamiflu®)). The update states that the vast majority of the reported adverse reactions are considered to be non-serious. The CHMP concluded that the benefit-risk profile of Celvapan, Focetria and Pandemrix continues to be positive.(Arepanrix® is not marketed in the Euroepan Economic Area (EEA)).

Consequently, the Committee recommended the further use of the vaccines in the authorized indication even after the pandemic was declared over. Details of the reported reactions are available on the EMA website.

(2) The EMA published the CHMP's conclusions on the possible risk of narcolepsy with the influenza vaccine Pandemrix. It was concluded that the available evidence was insufficient to determine whether there is any link between Pandemrix and reports of narcolepsy, and that further studies were necessary to fully understand this issue. It was agreed that at present the benefit-risk balance for Pandemrix continues to be positive, and that while the review is still ongoing, there was no need for Europe-wide restrictions on use. The ongoing review will require new observational (epidemiological) research in order to reach conclusions on whether there is a link between Pandemrix and narcolepsy. According to the Agency, up to 17 September 2010, there are 81 reports from health-care professionals suggestive of narcolepsy, and 15 consumer reports.

References:
(1) Twenty-second pandemic pharmacovigilance update, EMA, 19 August 2010 (www.emea.europa.eu).
(2) Press release, EMA, 23 September 2010 (www.emea.europa.eu).

Inhaled and intranasal corticosteroids

Risk of psychological and behavioural effects

UK. The MHRA warned that psychological and behavioural side effects may occur in association with use of inhaled and intranasal formulations of corticosteroids. These effects include psychomotor hyperactivity, sleep disorders, anxiety, depression and aggression (particularly in children). Inhaled corticosteroids are used for the prevention of asthma. Intranasal corticosteroids are used in the management of hayfever, allergy and some nasal conditions. The Agency advises health-care professionals that all patients or their carers should be informed of the important benefits of steroid treatment and should be advised of these safety issues.

***Reference**:*
Drug Safety Update, MHRA, Volume 4, Issue 2, September 2010 (www.mhra.gov.uk).

Isotretinoin

Risk of serious skin reactions

UK. Health-care professionals have been advised that erythema multiforme (EM), Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with isotretinoin, and may result in hospitalisation, disability, life-threatening events or death. Isotretinoin is used for the treatment of severe acne that is resistant to adequate courses of standard antibacterial or topical therapy. According to *Drug Safety Update*, the licence holder for the brand leader Roaccutane® identified a possible association between isotretinoin use and serious skin conditions including EM, SJS and TEN after a review of the data held in their global safety database. A total of 66 cases of severe skin reactions have been reported worldwide in association with isotretinoin as follows: 15 cases of SJS; 44 cases of EM (in four of which rash symptoms reoccurred when isotretinoin was reintroduced); five cases of TEN. The MHRA also advises that patients starting isotretinoin treatment should be informed of the signs and symptoms of these serious skin eruptions and advised to stop treatment and contact their health-care professional immediately if any of these arise.

(See WHO Pharmaceuticals Newsletter No.2, 2010 for warnings about severe skin reactions in Canada.)

Reference:
Drug Safety Update, MHRA, Volume 4, Issue 2, September 2010 (www.mhra.gov.uk).

Lithium

Risk of renal impairment associated with long term lithium use

New Zealand. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) reminded health-care professionals that long-term lithium therapy can cause renal failure along with other metabolic adverse effects including hypothyroidism, weight gain and hyperparathyroidism. According to *Prescriber Update*, the Centre for Adverse Reactions Monitoring has received a total of nine reports of renal failure in association with lithium use. Six of the reports were received in the last two years. The mean age of patients was 53 years (range 36 to 77 years). The average duration of lithium therapy prior to development of renal failure was 28 years (range 14 to 38 years). In at least one case, renal function continued to deteriorate despite lithium being discontinued. Medsafe emphasizes the importance of continued monitoring of renal function to ensure early detection and management of renal impairment, and advises that renal function, including glomerular filtration rate should be measured regularly even after 10 to 15 years of therapy.

Reference:
Prescriber Update Vol. 31, No.3 September 2010, (www.medsafe.govt.nz).

Monoclonal antibodies

Risk of systemic fungal infections

New Zealand. Medsafe warned that monoclonal antibodies, designed to suppress part of the immune system, can cause profound immunosupression in some patients, and that these patients are at risk of developing invasive fungal infections such as histoplasmosis, coccidioido-mycosis, candidiasis, aspergillosis, blastomycosis and pneumocystosis. Health-care professionals are advised to monitor patients closely during and after treatment for the development of signs and symptoms of systemic fungal infection. Symptoms include fever, malaise, weight loss, sweats, cough, dyspnoea, pulmonary infiltrates on x-ray and serious systemic illness.

Reference:
Prescriber Update Vol. 31, No.3 September 2010, (www.medsafe.govt.nz).

Nimodipine oral capsules

Serious medication errors from intravenous administration

USA. The US FDA reminded health-care professionals that oral nimodipine capsules should be given only by mouth or through a nasogastric tube and should never be administered intravenously. Nimodipine is used in a critical care setting to treat neurologic complications from subarachnoid haemorrhage and is only available as a capsule. The Agency warns that intravenous injection of nimodipine can result in death, cardiac arrest, severe decrease

in blood pressure and other heart-related complications. In 2006, a Boxed Warning was added to the prescribing information to warn against intravenous use of nimodipine. However, the Agency continues to receive reports of intravenous nimodipine use, with serious, and sometimes fatal, consequences.
Health-care professionals are also advised that if the nimodipine capsule cannot be swallowed, or if the patient is unconscious, a hole should be made in both ends of the capsule with an 18 gauge needle, and the contents of the capsule extracted into a syringe. To help minimize administration errors, it is recommended that the syringe be labelled "Not for IV Use". The needle should be removed from the syringe and the contents should then be emptied into the patient's *in situ* nasogastric tube and washed down the tube with 30 ml of normal saline (0.9%).

Reference:
FDA Drug Safety Communication, US FDA, 2 August 2010 (www.fda.gov).

Pioglitazone

Ongoing safety review on potential increased risk of bladder cancer

USA. The US FDA notified health-care professionals and patients that the Agency is reviewing data from an ongoing, ten-year epidemiological study designed to evaluate whether pioglitazone (Actos®) is associated with an increased risk of bladder cancer. Pioglitazone is approved as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. According to the Agency, the manufacturer has conducted a planned analysis of the study data at the five-year mark. Overall, there was no statistically significant association between the exposure to pioglitazone and bladder cancer risk. However, further analyses were performed looking at how long patients were on pioglitazone and the total amount of the medicine they received during that time. An increased risk of bladder cancer was observed among patients with the longest exposure to pioglitazone, as well as in those exposed to the highest cumulative dose of the medicine. The review is ongoing and the US FDA has not concluded that pioglitazone increases the risk of bladder cancer.

Reference:
FDA Drug Safety Communication, US FDA, 17 September 2010 (www.fda.gov).

Propolis

Reports of hypersensitivity reactions

New Zealand. Medsafe advised health-care professionals to consider the uncertain benefits of propolis versus the risk of developing hypersensitivity reactions or renal failure before recommending its use to patients. According to Prescriber Update, a review of international adverse reaction reports identified several cases of hypersensitivity reactions in people using complementary medicines containing propolis. The Agency states that patients with a history of allergies appeared to be at particular risk of these reactions. Propolis has also been associated with acute renal failure.

Reference:
Prescriber Update Vol. 31, No.3 September 2010, (www.medsafe.govt.nz).

Tocilizumab

Risk of fatal anaphylaxis

Canada. Hoffmann-La Roche Limited and Health Canada informed health-care professionals of the risk of fatal anaphylaxis associated with tocilizumab (Actemra®). Tocilizumab is authorized for intravenous use to reduce the signs and symptoms of moderately to severely active rheumatoid arthritis in adult patients who have inadequate response to one or more disease modifying anti-rheumatic drugs and/or tumour necrosis factor antagonists. The letter to health-care professionals states that a post-marketing case of fatal anaphylaxis has been reported in an elderly patient with a prolonged history of rheumatoid arthritis who was treated with tocilizumab. Prior treatments included methotrexate, sulfasalazine, azathioprine, etanercept, rituximab and abatacept. Concomitant medications included prednisone and leflunomide. Other medical history included hypertension for which the patient was being treated with a beta-blocker and ACE inhibitor. Health-care professionals are advised that if an anaphylactic or other serious hypersensitivity reaction occurs, administration of tocilizumab (Actemra) should be stopped immediately, and that appropriate medical management should be initiated and tocilizumab should be permanently discontinued.

Reference:
Advisories, Warnings and Recalls, Health Canada, 17 September 2010 (www.hc-sc.gc.ca).

Report from the Advanced Workshop for Consultants on Pharmacovigilance

6 – 10 September, Lomé, Togo

The WHO Consultants Network for Pharmacovigilance (PV) in Africa was created in 2007 to influence local PV knowledge and to leverage ongoing activities in one country for the benefit of others in the region. The Network has met for three consecutive years, twice in Ghana and once in Mozambique. The fourth meeting of the Network was held this year, in Lomé, Togo.

The Network was created at the initiative of the Department of Essential Medicines and Pharmaceuticals Policies, WHO HQ, in close collaboration with the WHO AFRO region and country offices. In addition to building regional capacity, the Network activities provide greater local visibility and put PV higher up on a country's 'medicines' agenda.

The meeting this year brought together consultants and experts in PV from Botswana, Burkina Faso, Cameroon, Ghana, Kenya, Morocco, Nigeria, Senegal, Sierra Leone, Tanzania, Togo and Zimbabwe; from WHO HQ, the WHO Collaborating Centre for International Drug Monitoring in Sweden (the Uppsala Monitoring Centre); and from the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Ghana (WHO CC, Ghana).

The aim of the Togo workshop was to sharpen the skills and expand the roles of the pool of experts in PV in order to offer support to the countries they represent and other public health initiatives. At the five day meeting, the network of pharmacovigilance consultants were empowered to offer help to neighbouring countries and to work more closely with the WHO CC, Ghana. The consultants received advanced training in the following areas:

- Ensuring the minimum requirements in a PV system
- Data management
- Signal detection
- Active surveillance methods such as cohort event monitoring
- Basic knowledge in Risk Management Plans
- PV in public health programmes
- Issues pertaining to safety monitoring of vaccines
- Role of PV centres in detecting medication errors
- Working with indicators for PV
- Fundraising
- Writing papers on PV

A PV 'tool kit' is being developed by the WHO CC, Ghana. The tool kit is a practical set of tools and supporting processes (with description of required resources), to facilitate PV enhancement in countries using Global Fund grant mechanisms and through various other global health initiatives. When fully developed the tool kit will be available to the public at *www.pvafrica.org*.

Pharmacovigilance (PV) has evolved over time in developed countries. Although inadequate infrastructure and limited resources (both financial and human) pose challenges to implementing PV in developing countries, increased vulnerability of local populations makes drug safety monitoring imperative. Establishing systems for PV in Africa will be the initial step. Assessment of strengths and weaknesses, expansion of existing infrastructure, and development of programs to educate, motivate, and provide feedback will be essential to help build capacity for PV. Standardizing methods of reporting, including approaches for defining events, determining severity, and assessing causal relationships will also be important. PV in Africa should be possible, but realistic assessment of the challenges and introduction of novel solutions will be needed to build sustainable programs.

The Network of experts for Africa that was established in 2007 with nine countries has grown steadily; in 2010 the Network was represented by experts and consultants from 15 countries (see fig. 1). With the training and emergence of experts in PV coupled with the establishment of the WHO CC, Ghana, there is extended room for PV technical assistance and support within the African region.

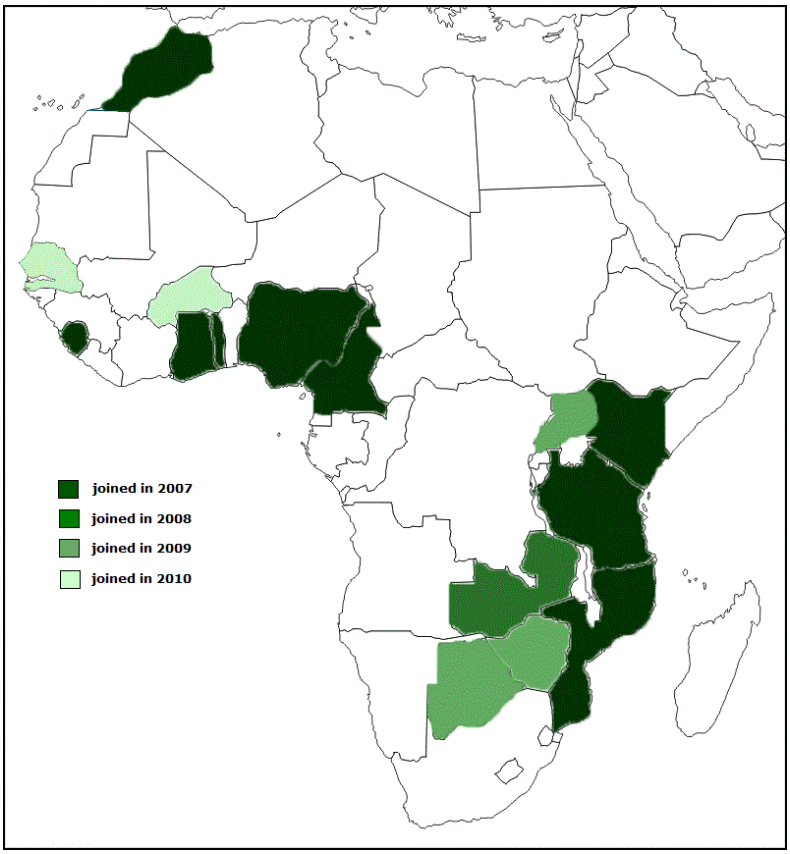


Figure 1: Countries Represented in the PV Consultants Network for Africa

Meeting of the Global Advisory Committee on Vaccine Safety

The Global Advisory Committee on Vaccine Safety (GAVCS), an expert clinical and scientific body, was established by WHO to provide independent, scientifically rigorous advice on issues of vaccine safety that potentially have global importance.

At its 22nd meeting 16-17 June, GACVS reviewed the safety of influenza vaccines; latest data on the finding of DNA from porcine circoviruses in rotavirus vaccines; the safety of live attenuated hepatitis A vaccines and the recently prequalified meningococcal A conjugate vaccine; and yellow fever vaccine risks.

Safety of influenza vaccines

The latest safety data on both pandemic and seasonal influenza vaccines were reviewed. With regard to pandemic A (H1N1) vaccines, to date the safety profile is reassuring, with no unexpected safety concerns identified. Most of the data reviewed comes from passive surveillance; data from active surveillance will be assessed as they become available. (Read also about the investigation of a potential relationship between A (H1N1) vaccination and narcolepsy in this issue the Pharmaceuticals Newsletter, page nine).

The Committee was also updated by Australia's regulatory authority regarding an increased number of reports of fever and febrile convulsions in children under five years of age following receipt of the 2010 seasonal inactivated influenza vaccine (Fluvax®) made by CSL. At the time of GAVCS meeting no clinical or epidemiological factors had been identified that explain the increase. Vaccine testing has shown no abnormalities, with additional testing ongoing. Given this situation, the Australian authorities have advised that Fluvax® 2010 seasonal influenza vaccine be suspended for healthy children less than five years of age. The Committee is not aware of reports of increased fever or febrile convulsions with other 2010 seasonal vaccines, but noted the importance of reviewing any available data on the use of 2010 seasonal vaccines elsewhere in the southern hemisphere, as well as data that will be forthcoming with the use of 2010 seasonal vaccines in the northern hemisphere.
(Read Safety Information News about this influenza vaccine from the US FDA on page nine)

Porcine circoviruses and rotavirus vaccines

GACVS reviewed new data related to the finding of porcine circovirus DNA in Rotarix® and RotaTeq®, two oral vaccines for the prevention of rotavirus gastroenteritis.

The safety of both Rotarix and RotaTeq is supported both by large pre-licensing clinical trials and extensive post-licensing safety experience. Worldwide, more than 69 million doses of Rotarix and 37 million doses of RotaTeq have been distributed. Given the extensive clinical data supporting the safety of both Rotarix and RotaTeq and the benefits of rotavirus vaccination for children, GACVS considers that the benefits of vaccination far outweigh any currently known risk associated with use of either rotavirus vaccine. GACVS will continue to review data as they become available.

Clinical safety profile of meningococcal A conjugate vaccine

The committee was given an update of clinical safety data from studies with a new meningococcal A conjugate vaccine (MenAfriVac) and of plans for mass vaccination campaigns to be launched in selected districts in Burkina Faso, Mali and Niger in September, and nationwide in the three countries beginning in December.

The Committee concluded that the data accumulated in clinical trials so far do not indicate any significant safety issues with the MenAfriVac vaccine. As the vaccine will soon be used in mass campaigns, the committee reiterated its previous advice that, where possible, a phased introduction of the vaccine would be desirable to accumulate additional safety data through careful post-marketing surveillance and it was pleased to note that such studies were being planned.

***Full report**:*
http://www.who.int/wer/2010/wer8530.pdf

Handling of complaints of prequalified medicines

Background

The WHO Prequalification of Medicines Programme and specifically its inspection team is responsible for handling and monitoring complaints regarding prequalified medicines. Complaints are managed in accordance with an internal WHO standard operating procedure (SOP).

General information

Definition of complaint of prequalified medicines

An expression of dissatisfaction and/or report of a quality defect related to prequalified medicine.Complaints are categorized as follows:

- product defect: a fault or deviation from the required attributes or variable characteristics of a product (e.g. non-compliance with the approved product specification or product contamination)
- quality-related problem/quality issue: a fault or event which may negatively impact the quality of a medicinal product
- adverse drug reaction (ADR)

Complaints are received from various sources:

- customers
- regulatory agencies
- procurement agencies

Complaints can be submitted to the Prequalification of Medicines Programme (PQP) by:

- phone:+41 22 791 2953, +41 22 791358, +41 22 7914344
- fax: +41-22-791-4730
- email: prequal@who.int
- Letter: WHO Prequalification of Medicines Programme; HSS/EMP/QSM World Health Organization; 20, Avenue Appia; 1211 Geneva, Switzerland

Each complaint is assigned a complaint number and recorded in the complaint registration log. Each complaint about a prequalified medicine is reported to the manufacturer for investigation and response to WHO.

Complaints are always followed up during routine GMP inspections. However, in some circumstances a special on-site inspection by a WHO inspection team may be required to investigate a complaint.

WHO PQP's Head of Inspections is responsible for overseeing handling of complaints. Upon receipt of a complaint a WHO PQP inspector is assigned to handle it.

Details of complaints received 2007–2009

In 2007, WHO PQP received and handled eight complaints, five of which were product quality related, two which were related to ADR and one which was related to the site non-compliance with GMP.

In 2008, WHO PQP received and handled three complaints, of which one was product quality related, one was related to the site non-compliance with GMP and one was related to the company web page.

In 2009, WHO PQP received and handled eight complaints, of which six were product quality related, one was related to company quality control laboratory equipment and one was related to the CRO where bioequivalence studies were performed.

Table 1. Complaints by year and type

Year	Number of product quality related complaints	Number of other complaints
2009	6	2
2008	1	2
2007	5	3

All product-related complaints for 2007–2009, except one, were related to the medicines that had been prequalified by WHO.

Complaints were received from:

- regulatory authorities
- procurement organizations
- manufacturing sites

The nature of the complaints was as follows:

- adverse drug reaction
- appearance of tablets
- assay out of specifications
- blister pack(s) missing some tablets
- friability out of specifications
- labelling error
- unpleasant smell of tablets
- dissolution out of specifications

Table 2. Total number of complaints for the years 2007–2009.

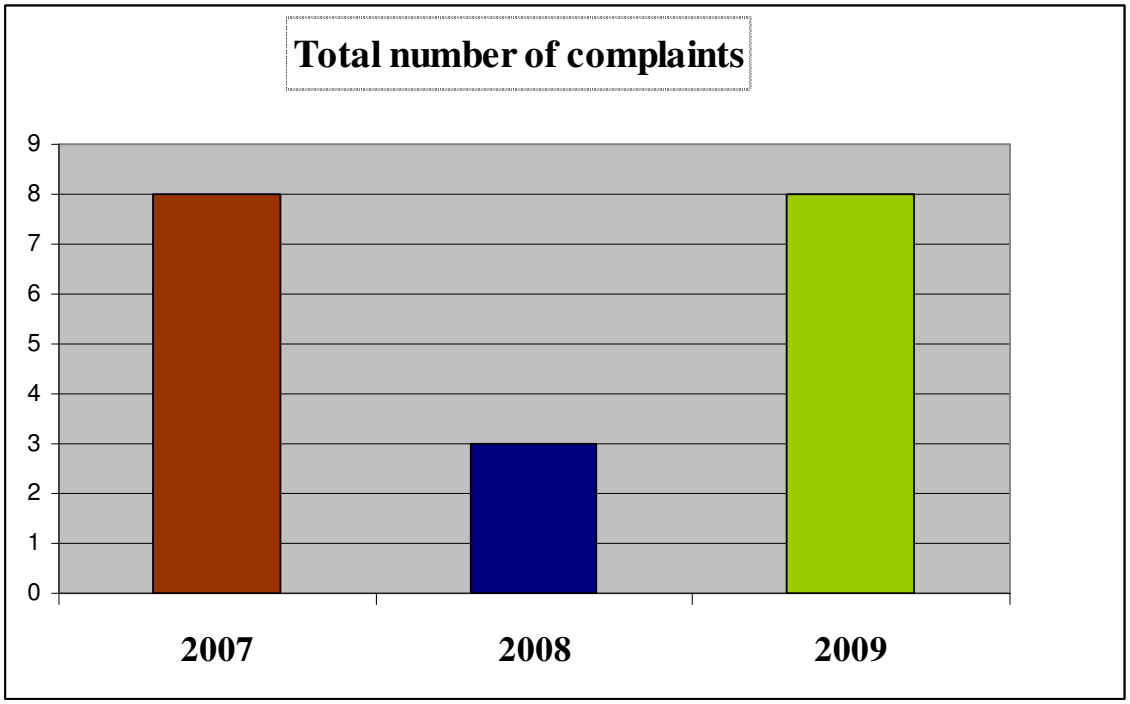
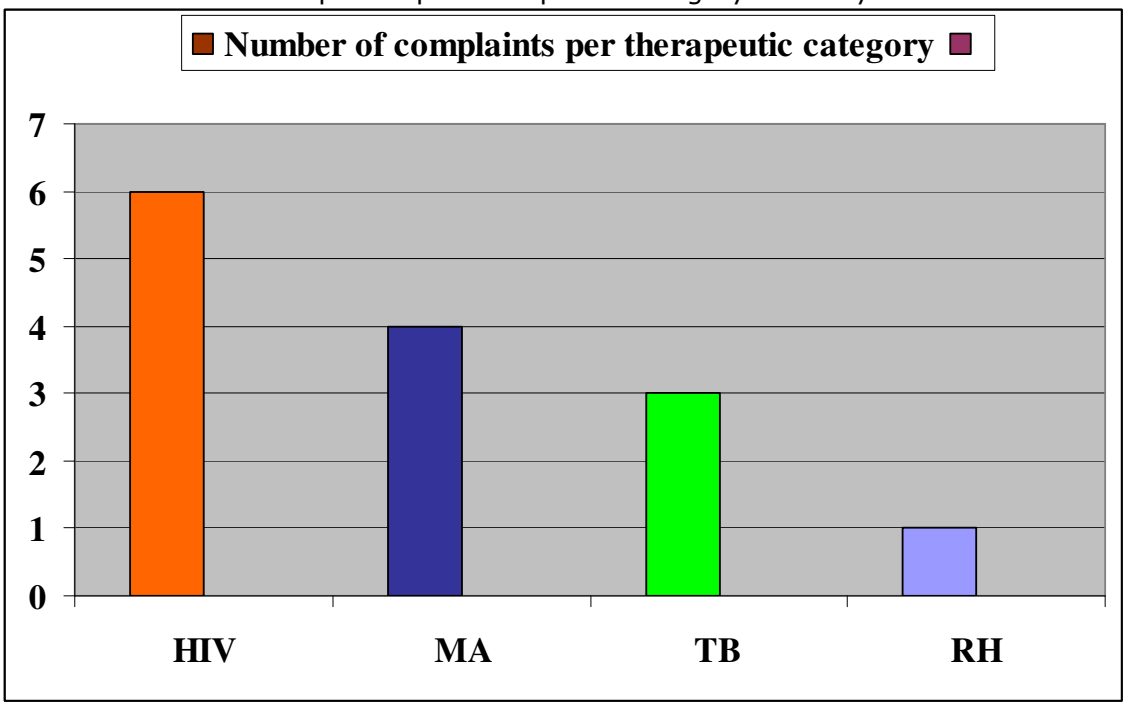


Table 3. Number of complaints per therapeutic category for the years 2007–2009.



Inspections were carried out to further investigate four complaints. All complaints were satisfactory closed out.