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:

Quality Assurance and Safety: Medicines, EMP-HIS, World Health Organization, 1211 Geneva 27, Switzerland, E-mail address: pals@who.int

This Newsletter is also available on our Internet website:

http://www.who.int/medicines

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring, Box 1051, 751 40 Uppsala, Sweden, Tel: +46-18-65.60.60, Fax: +46-18-65.60.80, E-mail: info@who-umc.org, Internet: http://www.who-umc.org

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world.

The feature article in this issue brings you the recommendations from the Thirty-fifth Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring, in Brazil, 11-14 November 2012.

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Botulinum Toxin

**New labelling information for all products**

**Canada.** Health Canada requested all manufacturers of botulinum toxin products currently available on the Canadian market revise their product labels to reflect that each product has its own individual potency and as such is not interchangeable with other botulinum products. This revision is to help prevent medication errors with the use of these products.

The labelling changes are due to a risk evaluation of the active ingredients (Clostridium botulinum toxin type A and type B) within these products. Botulinum toxins are produced by different manufacturing processes, are obtained by different techniques and are derived from different Clostridium strains. As a result of these differences, these products cannot be interchanged as these changes can cause unexpected side-effects.

Health Canada advised health-care professionals that the established drug names of the botulinum products have not been changed yet to emphasize the differing dose-to-potency ratios of these products. Manufacturers will have one year to comply with the labelling change requests.

**Reference:**
Advisories, Warnings and Recalls, Health Canada, 21 January 2013 ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca)).

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**Dabigatran etexilate mesylate**

**Contraindication in patients with mechanical prosthetic heart valves**

**USA (1).** The U.S. Food and Drug Administration (FDA) advised health-care professionals and the public that dabigatran etexilate mesylate (Pradaxa®) should not be used to prevent stroke or blood clots (major thromboembolic events) in patients with mechanical heart valves, also known as mechanical prosthetic heart valves. A clinical trial in Europe (the RE-ALIGN trial) was recently stopped because dabigatran users of the drug were more likely to experience strokes, heart attacks, and blood clots forming on the mechanical heart valves than were users of the anticoagulant warfarin. There was also more bleeding after valve surgery in the dabigatran etexilate mesylate users than in the warfarin users.

Dabigatran etexilate mesylate is not approved for patients with atrial fibrillation caused by heart valve problems by the US FDA. The US FDA is requiring a contraindication of the drug in patients with mechanical heart valves.

It is recommended that health-care professionals should promptly transition any patient with a mechanical heart valve who is taking dabigatran etexilate mesylate to another medication. The use of dabigatran etexilate mesylate in patients with another type of valve replacement made of natural biological tissue, known as a bioprosthesis, has not been evaluated and cannot be recommended. Patients with all types of prosthetic heart valve replacements taking dabigatran etexilate mesylate should talk to their health-care professional as soon as possible to determine the most appropriate anticoagulation treatment. Patients should not stop taking anticoagulant medications without guidance from their health-care professional; stopping dabigatran etexilate mesylate or other anticoagulants suddenly can increase the risk of blood clots and stroke.

**Canada (2).** Boehringer Ingelheim (Canada) Ltd., in consultation with Health Canada, has announced that dabigatran etexilate (Pradaxa™ and Pradax®) Product Monograph will be revised to include a new contraindication for use in patients with prosthetic heart valves requiring anticoagulant treatment due to their valvular status.

(See WHO Pharmaceuticals Newsletters Nos. 1, 3, 4 and 6, 2012 for previous related announcements).

**References:**
(1) FDA Drug Safety Communication, US FDA 19 December 2012 ([www.fda.gov](http://www.fda.gov)).
(2) Advisories, Warnings and Recalls, Health Canada, 21 December 2012 ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca)).

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**Domperidone**

**Serious ventricular arrhythmias and sudden cardiac death**

**Australia.** The Therapeutic Goods Administration (TGA) advised health-care professionals that domperidone (Motilium®) should be initiated at the lowest possible dose in adults. Recent epidemiological studies have shown that the use of domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death, particularly in patients taking daily doses greater than 30 mg, and in patients older than 60 years of age.
Patients should be advised to stop taking domperidone and seek immediate medical attention if they experience signs or symptoms of an abnormal heart rate or rhythm while taking domperidone. These include dizziness, palpitations, syncope or seizures.

Health-care professionals are advised that:

- Domperidone is contraindicated with ketoconazole, erythromycin or other potent CYP3A4 inhibitors which prolong QTc interval such as fluconazole, voriconazole, clarithromycin and amiodarone.
- Domperidone should be used with caution and at the lowest effective dose in at-risk patients such as those:
  - with existing prolongation of cardiac conduction intervals (particularly the QT interval)
  - using potent CYP3A4 inhibitors which may increase plasma levels of domperidone such as itraconazole, amphotericin, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, diltiazem, verapamil and aprepitant
  - with significant electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia)
  - with underlying cardiac diseases such as congestive heart failure.

The dose of domperidone may be adjusted upward with caution to achieve the desired effect as needed. The expected benefit of an increased dose should outweigh the potential risks. The maximum dose of domperidone is 80 mg.

Domperidone should not be used in children.

The Product Information for domperidone has been updated to include the new drug dosage and usage recommendations, as well as information about the risk of serious ventricular arrhythmias and sudden cardiac death.

(See WHO Pharmaceuticals Newsletter No.2, 2012 and No. 2, 2007 for association with serious ventricular arrhythmias and sudden cardiac death in Canada).

Reference:

Fingolimod

Cardiovascular safety risk

Australia. The TGA advised health-care professionals of important cardiovascular safety related changes to the fingolimod (Gilenya®) Product Information. Fingolimod is now contraindicated in patients with specific cardiac conditions and in patients with concomitant treatment with Class Ia or Class III anti-arrhythmic drugs during fingolimod initiation.

The Precautions section has been updated to include first-dose monitoring, with emphasis on cardiac monitoring, namely pulse, blood pressure and electrocardiogram. Should a patient require pharmacological intervention during the first-dose observation, overnight monitoring in a medical facility should be instituted and the first-dose monitoring strategy should be repeated after the second dose of fingolimod.

(See WHO Pharmaceuticals Newsletter No. 1, 2012 for safety review of a reported death after the first dose in the USA and for review of fingolimod and advise to intensify cardiovascular monitoring after first dose in EU, No. 2, 2012 in Canada and No.3 2012 for New advice to better manage risk of adverse effects on the heart in Europe and the US).

Reference:

Ondansetron

Product removal due to potential for serious cardiac risks

USA. The US FDA notified health-care professionals that the 32 mg, single intravenous (IV) dose of ondansetron hydrochloride (Zofran®) will no longer be marketed because of the potential for serious cardiac risks.

The 32 mg, single IV dose of ondansetron hydrochloride had been used to prevent chemotherapy-induced nausea and vomiting. A previous Drug Safety Communication (DSC), issued on June 29, 2012, communicated that the 32 mg, single IV dose should be avoided due to the risk of a specific type of irregular heart rhythm called QT interval prolongation, which can lead to Torsades de Pointes, an abnormal, potentially fatal heart rhythm. These drugs are sold pre-mixed in solutions of either dextrose or sodium chloride in plastic containers.

The US FDA continues to recommend the intravenous regimen of 0.15 mg/kg administered every 4 hours for three doses to prevent chemotherapy-induced nausea and vomiting. Oral dosing of Ondansetron remains effective for the prevention of chemotherapy-induced nausea and vomiting.

(See WHO Pharmaceuticals Newsletters No. 5, 2012 for risk of abnormal heart rhythms in the USA and Nos. 4 and 6)
2012 for dose restriction in intravenous use due to dose-dependent QT interval prolongation).

**Reference:**

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**Over-the-counter cough and cold medicines for children**

**Use in children**

**Australia.** The TGA has recently completed a review of the safety and efficacy of over-the-counter cough and cold medicines for use in children.

The Agency concluded that these medicines:

- should not be given to children under 6 years of age
- should only be given to children aged 6 to 11 years on the advice of a doctor, pharmacist or nurse practitioner
- should be labelled with warnings and instructions to the above effect
- should only be available in child-resistant packaging.

The TGA advised health-care professionals that no changes have been made to the scheduling of these medicines and a prescription is not required. A recommendation for treatment with these medicines for a child less than 6 years of age constitutes off-label use.

Existing stock with older labelling can still be sold for adults and children aged 12 years and over (or 6 to 11 years on the advice of a health professional) until stocks are exhausted.

**Reference:**

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**Sodium oxybate**

**Warning against use with alcohol or drugs causing respiratory depression**

**USA.** The US FDA reminded health-care professionals and patients that the combined use of sodium oxybate (Xyrem®) with alcohol or central nervous system (CNS) depressant drugs can markedly impair consciousness and may lead to severe breathing problems (respiratory depression). The use of alcohol with the drug is a new contraindication added to the sodium oxybate label, which already contraindicates its use with insomnia drugs. The use with other CNS depressant drugs (drugs that affect the CNS and may lead to breathing problems) such as opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, general anesthetics, and muscle relaxants should generally be avoided. The use of sodium oxybate along with these products or other CNS depressants increases the risk of breathing problems that may lead to loss of consciousness, coma, and death.

Sodium oxybate is approved to treat daytime sleepiness in patients with narcolepsy by the US FDA. Sodium oxybate is also known as gamma-hydroxybutyrate (GHB). GHB is a known drug of abuse that has been associated with central nervous system (CNS) adverse events, including death. Even at recommended doses, the drug can cause confusion, depression, and other neuropsychiatric events.

The US FDA urged health-care professionals to follow the dosing recommendations, contraindications, and boxed warning in the updated drug label and to avoid drug combinations that raise the risk of respiratory depression and death. Patients should not drink alcohol or take insomnia drugs.

**Reference:**

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**Statins**

**Risk of increased blood sugar levels and diabetes**

**Canada.** Health Canada informed of a labelling update for statins regarding the risk of increased blood sugar levels and a small increased risk of diabetes among patients already at risk for the disease. Based on the review of all available data, Health Canada concluded that the risk of diabetes appears to be mainly in patients with pre-existing risk factors for diabetes, such as high levels of glucose or triglycerides, obesity or high blood pressure. Health Canada continues to believe the overall cardiovascular benefits of statin drugs in reducing blood cholesterol outweigh their risks.

A new warning about the increased blood sugar levels and the risk of diabetes, including information on how to identify high-risk patients, has been added to the drug labels for the six statins currently marketed in Canada: atorvastatin (Lipitor® and generics), lovastatin (Mevacor® and generics), pravastatin (Pravachol® and generics), rosuvastatin (Crestor® and generics), simvastatin (Zocor® and generics), and fluvastatin (Lescol® and generics).

The new labels recommend that health-care professionals carefully monitor the use of statins in patients at a high risk of future diabetes.
Health Canada recommended patients who are on statins and experience symptoms associated with increased blood sugar, such as severe frequent urination, thirst or hunger, to contact their health-care professional.

Reference:

Telaprevir

New boxed warning - serious skin reactions

USA. The US FDA announced that it received reports of serious skin reactions, some fatal, in patients taking the hepatitis C drug telaprevir (Incivek®) in combination with peginterferon alfa and ribavirin (Incivek combination treatment). Some patients died when they continued to receive Incivek combination treatment after developing a worsening, or progressive rash and systemic symptoms (symptoms affecting the entire body). The US FDA added a boxed warning to telaprevir drug label stating that Incivek combination treatment must be immediately stopped in patients experiencing the above.

Telaprevir is a hepatic C virus NS3/4A protease inhibitor indicated in combination with peginterferon alfa and ribavirin for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including patients who have cirrhosis, are treatment-naïve, or who have been previously received interferon-based treatment.

Health-care professionals are recommended to make sure patients know that rash may occur with Incivek combination treatment, and explain the signs and symptoms of severe skin reaction and when to seek care. If serious skin reactions occur, all three components of Incivek combination treatment, including peginterferon alfa and ribavirin, must be immediately discontinued, and the patient should receive urgent medical care. Consideration should also be given to stopping any other medications that may be associated with serious skin reactions.

Reference:

Tolvaptan

Potential risk of liver injury

USA. The US FDA and Otsuka, the manufacturer of tolvaptan (Samsca®), notified health-care professionals of significant liver injury associated with the drug. In a double-blind, 3-year, placebo-controlled trial in about 1400 patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) and its open-label extension trial, 3 patients treated with the drug developed significant increases in serum alanine aminotransferase (ALT) with concomitant, clinically significant increases in serum total bilirubin. In the trials the maximum daily dose of tolvaptan administered (90 mg in the morning and 30 mg in the afternoon) was higher than the maximum 60 mg daily dose approved for the treatment of hyponatremia.

Most of the liver enzyme abnormalities were observed during the first 18 months of therapy. Following discontinuation of treatment, all 3 patients improved. These data are not adequate to exclude the possibility that patients receiving tolvaptan for its indicated use of clinically significant hypervolemic and euvolemic hyponatremia are at increased risk for irreversible and potentially fatal liver injury.

The US FDA recommended that health-care providers should perform liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. If hepatic injury is suspected, tolvaptan should be promptly discontinued, appropriate treatment should be instituted, and investigations should be performed to determine probable cause. tolvaptan should not be re-initiated in patients unless the cause for the observed liver injury is definitively established to be unrelated to treatment with tolvaptan.

Reference:

Zolpidem containing products

Lower recommended doses required

USA. The US FDA recommended that the bedtime dose of zolpidem be lowered because new data show that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. This announcement focuses on zolpidem products approved for bedtime use, which are marketed as generics and under the brand names Ambien®, Ambien CR®, Edluar®, and Zolpimist™.

Data showed that the risk for next-morning impairment is highest for patients taking the extended-release forms of these drugs (Ambien CR® and generics). Women appear to be more susceptible to this risk because they eliminate zolpidem from their bodies
more slowly than men. Because use of lower doses of zolpidem will result in lower blood levels in the morning, the US FDA required the manufacturers of these drugs to lower the recommended dose. The recommended doses of Intermezzo®, a lower dose zolpidem product approved for middle-of-the-night awakenings, are not changing. At the time of Intermezzo’s approval in November 2011, the label already recommended a lower dosage for women than for men.

The US FDA reminded the public that all drugs taken for insomnia can impair driving and activities that require alertness the morning after use.

The US FDA recommended that:

- The dose of zolpidem for women should be lowered from 10 mg to 5 mg for immediate-release products (Ambien®, Edluar®, and Zolpimist™) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR®).
- For zolpidem and other insomnia drugs, the lowest dose that treats the patient’s symptoms should be prescribed.
- Patients should be informed that impairment from sleep drugs can be present despite feeling fully awake.

The US FDA is continuing to evaluate the risk of impaired mental alertness with other insomnia drugs, including over-the-counter (OTC) drugs available without a prescription.

Reference:
Carbamazepine, oxcarbazepine and eslicarbazepine

Potential risk of serious skin reactions associated with the HLA-A*3101 allele.

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) reported that the risk of serious skin-related adverse drug reactions, including Stevens-Johnson syndrome, occurring with carbamazepine (Tegretol®) may be increased in the presence of the HLA-A*3101 allele in patients of European descent or Japanese origin. Human leukocyte antigens (HLA) are involved in some drug-specific abnormal immune responses including SJS and TEN, and the HLA allele HLA-B*1502 is known to be highly associated with carbamazepine-induced SJS and TEN in certain Asian populations. More recently, a new genetic marker, HLA-A*3101, has been identified in Japanese individuals and individuals of European descent for serious carbamazepine-induced cutaneous adverse drug reactions such as SJS, TEN, and drug rash with eosinophilia (DRESS), and less severe reactions such as acute generalised exanthematous pustulosis (AGEP) and maculopapular rash.

However, there are currently insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine or chemically-related medicines. Patients of European descent or Japanese origin who are known to be positive for this allele should only receive carbamazepine, oxcarbazepine (Trileptal®) or eslicarbazepine (Zebinix®) after careful consideration of the benefits and risks.


Varenicline

Updated safety review on the risk of cardiovascular adverse events

USA. The US FDA informed the public about the results of a large, combined analysis (called a meta-analysis) of clinical trials that compared patients who received the smoking cessation drug varenicline (Chantix®) to patients who received a placebo. A higher occurrence of major adverse cardiovascular events (a combined outcome of cardiovascular-related death, nonfatal heart attack, and nonfatal stroke) was observed in patients using the drug compared to placebo. These events were uncommon in both varenicline and placebo groups, and the increased risk was not statistically significant, which means it is uncertain whether the excess risk for the varenicline group was due to the drug or due to chance.

Health-care professionals are advised to weigh the risks of varenicline against the benefits of its use. It is important to note that smoking is a major risk factor for cardiovascular disease, and the drug is effective in helping patients to quit smoking and abstain from it for as long as one year. The health benefits of quitting smoking are immediate and substantial.

Patients are advised to contact their health-care professional if they experience new or worsening symptoms of cardiovascular disease, such as chest pain, shortness of breath, calf pain when walking, or sudden onset of weakness, numbness, or difficulty speaking. Patients should also contact their health-care professional if they have any questions or concerns about varenicline.

(See WHO Pharmaceuticals Newsletters No. 4, 2011 for risk of certain cardiovascular adverse events with varenicline in the USA).

Recommendations from the Thirty-fifth Annual Meeting of National Pharmacovigilance Centres

The Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring was held in Brazil, 11-14 Nov 2012. At the meeting eight working groups discussed various pertinent issues in pharmacovigilance (PV). A summary of these discussions is provided.

1. Good Management Practices for national PV centres

Pharmacovigilance is a science that needs good management practices to ensure that the aims and objectives of a country’s National PV system are met in the light of limited resources.

The group discussed the principles of good management practices and how and why they should be applied to pharmacovigilance. The following recommendations were made.

National PV centres to:
1. Harmonize activities on a global level (coordinated by WHO/UMC)
2. Collaborate with other national centres at the regional level
3. Support each other and share experiences.

WHO and its Collaborating Centres to:
1. Provide guidance on grant applications
2. Provide a list of all available PV resources, with web links, updates and processes to access these resources

2. Wider access to data in WHO database: optimizing data utilization via VigiLyze

The objective was to discuss the optimal use of information and data extracted from the WHO Individual Case Safety Reports (ICSR) database. Four different user ‘personas’ were identified with distinct needs and use of the database information: the user group that needs easy-to-use interface with instant information on specific medicines issues; senior management who need evidence to provide / request funding and collaborations; the intermediate group that needs the information for decision making; and the general user group with a broad interest in the information. The group concluded that the first version of VigiLyze, the new search and statistics tool being developed by the Uppsala Monitoring Centre (UMC), needs to first address the requirement of the most immediate user from within these personas. The following recommendations were made.

1. UMC to focus on the needs of the front-line user in the first phase of VigiLyze development
2. Needs of other users should be considered in future releases
3. A user/working group should be set up to establish user groups, confirm needs and further refine VigiLyze.

3. Building capacity for safety monitoring of new vaccines

Although, hundreds of millions of doses of vaccines are used every year in developing countries, assessments by WHO demonstrate that some countries still do not have the ability to monitor and ensure the safe use of vaccines. This working group discussed capacity building for monitoring adverse events following immunization (AEFI). The group agreed that effectiveness and safety of vaccines might vary across countries.

The following recommendations were made.
1. WHO to improve the availability of background data in low and middle income countries (LMIC) by pooling placebo data from clinical trials

2. National centres and countries to improve collaborations between medicines and vaccines PV systems; and share experiences on the introduction of new vaccines in their settings

3. Both national centres and WHO to:
   1. Offer more training and build capacity in vaccine PV, especially in LMIC
   2. Translate the ‘online’ WHO vaccine PV course into more languages
   3. Develop and implement new methodologies in AEFI data collection, causality assessment and signal detection

4. The ATC/DDD system: a tool linking drug consumption and adverse drug reaction data

The Anatomical, Therapeutic and Chemical (ATC) classification system and the Defined Daily Dose (DDD) are recommended by WHO for measuring drug utilization in countries. The WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway (WHO CC, Oslo), develops and maintains the ATC/DDD system.

The objective of this working group was to ascertain ways of raising awareness and promoting the use of the ATC/DDD system in PV. The following recommendations were made:

WHO and national centres to:
   1. Organize capacity building and training activities for implementing ATC/DDD
   2. Build links between medicine consumption and adverse drug reaction databases
   3. Promote use of ATC/DDD in studying and sharing data on consumption and trends in use of specific drugs such as sibutramine; monitor the use of medicines in children in chronic diseases.

5. The PV Toolkit and its further development

The PV Toolkit is a collection of resources and information needed for the practice of PV. The main aim is to ensure that PV practitioners get access to information on the processes and activities involved in PV from a reliable source.

The group discussed the further development of the Toolkit. The following recommendations were made.

WHO/WHO Collaborating Centre for Training and Advocacy in Pharmacovigilance, Accra, Ghana should
   1. Facilitate the translation of the Toolkit into various WHO official languages
   2. Include a URL link to all National PV centres in the Toolkit
   3. Make the Toolkit more interactive and user friendly
   4. Use the Toolkit as a platform for sharing experiences amongst national centres
   5. Promote the Toolkit to all national centres through advocacy
   6. Include Information on pharmacovigilance for special groups such as children and the elderly
   7. Include standard PV training modules in the Toolkit for national centres

6. Centralized or decentralized PV system –Pros and Cons

This working group discussed the pros and cons of both centralized and decentralized PV systems, examples of such models in countries and challenges faced in implementing and maintaining such systems. A centralized model provides a single point of entry for information, with less financial needs; however there is decreased patient accessibility and less effective communication to health professionals. A decentralized system on the other hand is more accessible to patients and improves communication. However, decentralizing requires coordination, more funding and resources for capacity building. It was concluded that the choice of having a centralized or decentralized system will depend on the size of the country, complexity of the national health system and support from government authorities and other key stakeholders. The
group recommended that WHO should develop guidelines on setting up centralized and decentralized PV systems, highlighting the pros and cons of each system.

7. The role of industry in national PV programmes

The objectives of PV within the industry are essentially the same as those of regulatory agencies; that is, to protect patients from unnecessary harm by identifying previously unrecognized drug hazards, elucidating predisposing factors, and quantifying risk in relation to benefit. Although the perspectives of companies and the regulatory agencies may be different, they now work more and more closely together and share information. The objective of the working group was to discuss the challenges and value for national pharmacovigilance programmes in collaborating with industry. The group recommended that national centres should:

1. Provide guidance to Industry on obligations, procedures and protocols
2. Perform independent research in certain cases
3. Have the ability to monitor Marketing Authorization Holders (MAHs) risk minimization activities and obligate the MAH to carry out post-marketing studies.
4. Engage in open communication with industry

8. Harmonizing PV with health economics for outcome measurements – setting the research agenda

PV is a form of intervention in the healthcare system with economic benefits, to the system, to individuals and to society. Health economics analysis (HEA) can demonstrate the cost-effectiveness of PV but only few studies have been done in this regard. The working group discussed savings to health expenditure through PV and how the cost-benefit of PV could be measured. The following recommendations were made.

WHO to:
1. Develop guidelines or protocols and standardized methods for studying the cost benefit of PV
2. Promote the concept of cost-benefit of PV and its measurement in PV training programmes

National Centres to:
1. Carry out studies to establish the cost-benefit of PV activities