WHO Drug Information

Contents

Regulatory Issues

Drug regulation in 2006: vision and challenges

The Twelfth International Conference of Drug Regulatory Authorities (ICDRA) held in Seoul, Republic of Korea, from 3 to 6 April 2006 has once again provided drug regulators with a unique opportunity to meet and discuss the particular challenges of medicines regulation. The continuing need to harmonize and strengthen collaboration is underscored by the increasing complexity of the medicines market and technical skills needed to regulate innovative products. The latest ICDRA was hosted by the Korea Food and Drug Administration in collaboration with the World Health Organization. The event was highly appreciated by developed and developing countries for its continuing role in fostering a regulatory forum where matters of urgency and international relevance can be openly debated. On this occasion, the event led to adoption of the following recommendations which regulators consider important in assuring the quality, safety and efficacy of medical products.

International Conference of Drug Regulatory Authorities (ICDRA): recommendations

Access to medicines: new regulatory pathways for public health needs

1. In the assessment of products, particularly those developed for public health needs, countries should make use of new regulatory pathways provided by highly-evolved regulatory agencies in order to avoid duplication of effort. This would enable optimal use of limited resources.

2. In cooperation with well resourced regulatory agencies, WHO is urged to assist Member States to provide training on the best use of regulatory information on product approvals available in the public domain.

3. WHO should continue its efforts to prequalify active pharmaceutical ingredients for medicines for priority diseases, including HIV/AIDS, malaria and tuberculosis. Information concerning prequalified products and approved sites should continue to be made public in the form of WHO public inspection reports.

4. WHO should assist national regulatory agencies to develop innovative approaches to improve access to safe and effective essential medicines of quality which address public health needs.

Emerging diseases and crises management: regulatory challenges

1. The fight against emerging diseases requires global collaboration and multidisciplinary effort. Member states should ensure their national regulatory agencies are closely involved in national strategic decision making processes and are engaged as key stakeholders in national contingency planning. In this context, national regulatory agencies should develop business continuity plans and may also have a role in facilitating vaccine and pharmaceutical research and development, and development of blood screening tests.

2. WHO should take a leading role in the global preparedness for pandemic infections. Central to its role as the global leading health agency, WHO should cooperate with Member States to ensure transparency of epidemiological information, co-ordinate information and technology transfer on clinical trials and research and assist Member States through developing WHO standards for pre-marketing

evaluation of pharmaceuticals developed for pandemic use. It is important for national regulatory agencies to find mechanisms to share clinical trial results and epidemiological data. National regulatory agencies should not allow the threat of pandemics to compromise the principles of safety, efficacy and quality of vaccines and pharmaceuticals being considered for licensing approval.

3. National regulatory agencies should ensure that robust post-marking surveillance systems are in place to ensure that pharmaceuticals approved during a pandemic will continue to be closely monitored and subject to further assessment of their safety, efficacy and quality. To achieve this, national regulatory agencies should work with, among others, authorities for disease surveillance and the vaccine and pharmaceutical industry as close partners.

4. During a pandemic, the demand for blood and blood products is likely to increase. On the other hand, there could be lack of blood donations because of high morbidity and mortality of prospective donors. WHO should assist Member States -when drawing up contingency plans to include measures to maintain the integrity of their blood transfusion system, the continued supply of blood and blood products, and maintain transparency and information sharing.

New challenges in safety of medicines

High-profile drug safety issues present numerous challenges for drug regulators. New ways to improve knowledge about benefit/risk assessment, methods of signal detection, and communications to health professionals and the public are continually being sought. Spontaneous adverse drug reaction reporting has long been the cornerstone of pharmacovigilance and continues to serve a vital function, but changes in public expectations and drug development are encouraging regulators to think about pharmacovigilance as early as possible in the product life cycle.

The aim of pharmacovigilance planning is to provide regulators with a proactive approach to filling in knowledge gaps, while also improving the probability of detecting important safety signals as early as possible. Ultimately, this will result in better treatment choices for patients as they and their caregivers will have better information upon which to make choices. Furthermore, the publication of various risk management guidances, the improvement of scientific methods of adverse event signal detection and better and earlier communication of drug safety concerns to health professionals and the public are being developed. In addressing challenges of obtaining quality adverse event reports, cooperation between regulatory agencies and communicating effectively with the public are foremost.

Member States should:

1. Develop ways to ensure early communication to the public when an emerging safety concern arises.

2. Give patients, healthcare professionals and consumers quick and easy access to the most up-to-date and accurate information on medicines.

3. Encourage participation in WHO activities for reporting and collecting adverse reactions to medicines and vaccines, and seek ways to enhance reporting rates.

4. Improve scientific methods of adverse event signal detection.

WHO and Member States should:

5. Encourage pharmacovigilance planning in all public health programmes wherever possible.

WHO should:

6. Encourage cooperation between regulatory authorities when a new signal emerges.

Herbal medicines: safety through quality

1. Quality control of herbal medicines is complicated and difficult, and high-technology could be of valuable support. However, when country capacity is limited, continued use of dependable basic technical methods and tests is recommended.

2. Governments should provide adequate support for clinical studies, since there are few clinical studies and appropriate approaches for the assessment of efficacy. WHO should

provide technical guidance of appropriate approaches for clinical studies and assessment of efficacy of herbal medicines.

3. Traditional medicine plays an important role in primary health care in many developing countries and countries should consider categorizing herbal medicines based on available knowledge and the literature. Relevant appropriate requirements should be established for the assessment of safety and efficacy for different categorized herbal medicines to reduce cost and expenditure and meet demands of accessibility and affordability.

4. A challenge for national health authorities is the lack of research information and data on herbal medicines. Sharing national information and experience, as well as setting up common accepted standards through bilateral recognition and through international and regional regulatory cooperation for herbal medicines should be considered. WHO should continue to provide support to international and regional regulatory cooperative initiatives for herbal medicines.

5. In order to ensure safe and effective use of traditional medicine, integration of traditional medicine into national health systems should be considered where appropriate.

Good Review Practices

1. WHO should continue supporting country efforts to improve regulatory review processes in the context of overall improvement and implementation of good regulatory practices. Special emphasis should be given to helping small regulatory authorities; existing models may need to be adapted to match the resources available.

2. Regulators should make efforts to implement good review practices in order to improve regulatory systems through the introduction of good regulatory practices. Regulators should consider the road map approach, standardized formats for dossiers, disclosure of information, use of outside consultants, and quality management systems as useful tools for the improvement of review practices.

Bioequivalence: from science to practice

During recent years, the concept of bioequivalence has developed and several new regulatory approaches and guidance documents have been created. WHO has developed a comprehensive updated package of regulatory guidelines in line with former ICDRA recommendations.

1. Countries intending to implement bioequivalence requirements should consider learning from other countries' experience and take a risk based approach to implementing bioequivalence.

2. WHO is encouraged to assist Member States by providing training for regulators and industry on the implementation of the newly adopted WHO guidelines on the establishment of interchangeability (including guidelines on registration requirements to establish interchangeability of multisource (generic) pharmaceutical products, a proposal to waive in vivo bioequivalence requirements for some of the immediate release solid dosage forms in the WHO Model List of Essential Medicines, guidelines for organizations performing in vivo bioequivalence studies and a revised list of international comparator products).

Regulation of blood and blood-derived products: global challenges

Assurance of safe and adequate blood supplies nationally and regionally requires effective regulation and continuous vigilance. The preparation of blood components as well as plasma derivatives should be subject to established regulatory standards and controls. Essential elements of blood and blood product regulation include implementation and enforcement of good manufacturing practices (GMP), evaluation of blood donor screening tests, blood related drugs and medical devices, and the establishment of effective pharmacovigilance systems. In order to support development of these activities in countries with limited resources, it is essential to strengthen international approaches to regulation and to encourage the collaboration of national regulatory agencies at both regional and global levels.

1. Effective regulatory oversight is essential to ensure the quality and safety of blood and blood products. However, this cannot be achieved in the absence of a national legal framework and policy. Countries should take an active role in updating their respective legal provisions so that the implementation and enforcement of GMP for blood establishments can be made effective. WHO should provide, upon request, technical advice to those countries wishing to update legal provisions to strengthen the regulation of blood and blood products.

2. WHO should continue to give the highest priority to strengthening educational programmes and to providing training opportunities to support implementation and enforcement of GMP in national blood and plasma establishments. Appropriate guidance documents should be developed and/or updated. Countries should take an active role to ensure the implementation and enforcement of GMP for blood and plasma establishments as a prerequisite for consistent quality in the preparation of blood and blood products

3. WHO should continue to enable/promote cooperative interaction among national and regional regulatory authorities. In particular, WHO should:

- continue to support the development of a cooperative network for leading regulatory agencies, and

- facilitate the creation of regional networks of national authorities involved in the regulation of blood and blood products in order to enhance the regulatory role and leverage technical expertise.

4. Countries should take an active role in the operation of networks and regional steering committees should be established to promote harmonization of national regulatory policies. Appropriate support should be provided to this activity by WHO.

5. WHO should promote and encourage the establishment of effective pharmacovigilance systems for blood and blood products and link these to existing pharmacovigilance systems for medicines. Countries should implement and enforce appropriate and well structured reporting mechanisms for serious or unexpected adverse reactions to blood and blood products, including infectious transmissions. To enable safety investigations, countries should implement and enforce traceability with linkage from blood donor to recipient and from recipient to blood donor.

6. Regulatory authorities should encourage scientific studies to establish medical evidence in support of product labelling for clinical use. Suboptimal use of blood and blood products leads to wastage of precious products and increases the risk of side effects for recipients.

7. WHO should continue to strengthen the development of international reference materials and standards for validation and control of blood donor screening tests, especially for detection of anti-hepatitis C and anti-HIV antibodies.

8. WHO should encourage the development of risk-based regulatory strategies. Countries should consider establishing mechanisms and share information in this regard.

Role of regulators in control of advertising and promotion

1. Regulators should strengthen their efforts to ensure that advertising and promotion is in accordance with the approved product information and respective national regulations. To this end, regulators should collaborate closely with industry, publishers, the media and consumers. Such co-regulation of promotion must be underpinned by sound legislation and regulatory sanctions. Sanctions should be made public.

2. The global nature of the Internet is difficult to regulate. Regulators need to work together to control sources of Internet advertising. In addition, regulators should provide independent consumer and prescriber information on the Internet to support the quality use of medicines. This information should be easy to locate and be recognizable by prescribers and consumers. WHO is requested to continue to support countries in this regard.

3. WHO should increase its efforts to disseminate and promote the WHO Ethical Criteria for Medicinal Drug Promotion, in particular the provisions to ban direct-to-consumer advertising of prescription-only medicines and regulate

free samples to medical doctors. These criteria need to be actively supported by national regulatory agencies and used as the basis for national regulations. In this regard there needs to be close alignment between the regulation of promotion of medicines, foods and cosmetics.

Access to treatment for severe pain: what can regulators do?

1. Regulators should make efforts to ensure that national regulatory frameworks do not impose an excessive (i.e. not prescribed by the respective international conventions) administrative and legal burden on achieving access to internationally controlled narcotic painkillers.

2. To achieve better access to narcotic painkillers, and primarily those on the Model List of Essential Medicines, regulators are encouraged to work closely with international organizations such as the International Narcotics Control Board (INCB) and WHO, as well as with national and local bodies involved in palliative care. All severe pain needs to be appropriately addressed therapeutically and especially severe pain in life-limiting illnesses (cancer, HIV/AIDS).

3. Regulators should seek proactive ways to collaborate with other national health authorities to improve access to painkillers controlled under international conventions from importation/manufacture, through secure distribution chains, rational prescribing and dispensing to patients. To cover the population in need, it is necessary to widen patient access to legitimate prescribers, taking into account the national specific situation, e.g. consideration should be given to allowing specialized palliative care nurses or clinical officers to prescribe oral morphine.

4. WHO should support countries in improving their regulatory systems in order to identify potential administrative and legal hurdles to access of narcotic painkillers and find ways to eliminate these without compromising control functions prescribed by international conventions.

5. WHO should contribute to organizing respective regional and national training courses and exchange information on effective interventions carried out by countries that have achieved improvement in making narcotic painkillers more accessible to patients in need.

Pharmacoeconomics and regulation

Pharmacoeconomics is a discipline established to relate and identify the benefits and costs of medicines therapies. In the public sector, the aim is to inform and support decision-making in purchasing, pricing or reimbursement of medicines and to aid in clinical choice and guidance. Some of the main challenges encountered in setting up pharmacoeconomic mechanisms include questions about the clinical data and legal/ scientific issues, and availability of capacity/ resources,

Member States should:

1. Strive for open access to clinical regulatory data.

2. Be transparent about the criteria used in decision-making. If pharmaco-economics is one of them, provide clear methodological guidance.

3. Consider the need for active comparator studies and outcome data (to allow rational use of medicines) in pre-/post-authorization phases of regulatory assessment.

4. Consider the possibility to initiating/supporting independent comparative outcome studies.

WHO should:

5. Assist in high-level awareness-building.

6. Assist in capacity building.

7. Support regional networks.

8. Provide guidance on basic pharmaco-economic evaluation to the relevant national health authorities.

Global challenges for regulation of vaccines and other biologicals

Biological medicines are one of the fastest growing sectors of the pharmaceutical industry. Regulation of biologicals presents special challenges due to the specificities introduced by the biological nature of the products and

processes. Problems include the inherently variable nature of the starting materials and production systems which at some stage are derived from, or use, living organisms. Certain products, such as attenuated vaccines, consist of live organisms. The test methods needed to characterize products are biological (bioassays) and thus require special standardization efforts. Biologics research by the regulator may be necessary. Batch-related problems or accidents associated with biologicals have occurred and thus batch-by-batch regulatory review is necessary. Furthermore, the complexity of biologicals is increasing and some potential applications, such as gene therapy or cell and tissue therapy, are at the very leading edge of scientific development. Finally, a paradigm shift is occurring where biologicals, such as vaccines that will be used globally, are increasingly being manufactured and first licensed in countries with the highest disease burdens. This is placing extra responsibilities on regulators in such countries, often in the context of limited regulatory resources.

1. Countries are requested to ensure that biologicals receive science-based, innovative, and special regulatory attention. Regulatory collaboration is encouraged to support regulatory research and, further, to support countries without comprehensive biologicals regulatory systems. WHO should facilitate the process through establishment of regional and global networks of regulators.

2. WHO is requested to develop global regulatory consensus and guidance for biosimilars, which are a reality in several countries and will be a major regulatory challenge in the years to come.

3. Countries are encouraged to establish regional networks of national control laboratories (NCLs) to overcome the constraints that NCLs are facing now and in the future. WHO is requested to facilitate the work of NCLs through a global review of batch release strategies.

4. Countries are requested to increase their support for the development, characterization and distribution of biological reference preparations, which are an essential tool in the regulation of biological medicines. WHO is requested to ensure sustainability of it's international biological reference preparation programme.

5. Vaccines are increasingly being first trialed in countries with the highest disease burden. Countries should ensure that regulatory review of new vaccine applications includes the quality and pre-clinical, as well as clinical, parts of the dossiers. WHO should extend its support for capacity building to include quality and pre-clinical evaluation.

6. New combination vaccines are increasingly being produced in developing countries and present special regulatory challenges. WHO is requested to develop guidance on the quality, safety and efficacy evaluations of combination vaccines, including advice on bridging studies when combination vaccines are used in new populations.

Stability: global challenges for harmonization

Efforts regionally and interregionally to harmonize stability testing conditions offer many challenges, particularly for the hot and humid zone conditions. The question has generated much debate as to proper temperature and humidity conditions in relation to predicting the proper shelf life of a medicinal product within a country.

1. Member States should identify their stability testing conditions in order to facilitate import to and export from their country. Ideally these should be based on conditions currently in use, thus avoiding creation of barriers to access to medicines

2. Member States should make information available to WHO regarding stability conditions to be used within their markets.

3. WHO should make available country information in order to facilitate accessibility by manufactures and any interested party on an international basis.

4. WHO should observe the stability situation and any future developments and continue its efforts to find harmonized conditions, in light of any major changes to the current situation in regions.

5. Any international mechanism or organization which develops guidance relevant for countries outside their own regions should ensure that those countries are made aware of these developments and are directly approached to take part in the consultation process. For the International Conference on Harmonization (ICH), the Global Cooperation Group should be stressed as a way to work with regional harmonization initiatives.

Counterfeit medicines: toward better structured international collaboration

The 12th ICDRA congratulates WHO for the conference organized in Rome in February 2006 following-up on the recommendations of the 11th ICDRA and endorses the Declaration of Rome.

The 12th ICDRA welcomes the establishment of the International Medical Products Anti-Counterfeiting Task Force (IMPACT) and congratulates WHO on establishment of the IMPACT Secretariat.

The 12th ICDRA expects IMPACT to:

1. Work on the basis of terms of reference that should take into account the topics raised in the Rome Declaration and at the 12th ICDRA and should provide clear milestones and tangible results.

2. Develop concrete and pragmatic proposals on how to improve national, regional and international strategies to combat counterfeit medicines.

3. Analyse in particular how to improve the sharing of information on cases of counterfeit medicines taking into consideration existing systems, e.g. WHO Rapid Alert System.

4 Take into consideration existing activities in order to use the synergies of such activities and avoid duplication of effort.

5. The 12th ICDRA calls upon WHO to provide all necessary support to IMPACT via its Secretariat.

6. It calls upon the national and regional authorities to fully support IMPACT by providing the necessary resources during its work and by implementing its recommendations.

Small model drug regulatory authorities

1. Small national drug regulatory authorities (DRAs) should establish appropriate regulatory structures that correspond to the situation of the country without compromising minimum standards of safety, quality and efficacy, and should also attune legislative and administrative practices to the resources at the DRA's disposal.

2. Regulatory activities should be prioritized to develop and build up the registration and regulatory system in a stepwise manner, but continue to expedite access of essential medicines to the country's population.

3. Small DRAs should identify appropriate best practices for implementation that can be adopted or adapted to their situations by studying reference countries and suitable benchmark authorities.

4. Small DRAs should engage proactively in international cooperation, both at regional and global levels.

WHO should:

5. Consider convening a forum of small DRAs to facilitate sharing of information and best practices, including (a) leveraging on safety, quality and efficacy information available from larger, trusted authorities; (b) identifying trusted sources of generic medicines; and (c) standardizing formats for sharing of data about registered medicines in various national jurisdictions.

6. Continue to encourage the benefits of regional networks wherein smaller regulators can work with trusted larger regional authorities in order to optimize resources and enhance regulatory capacity.

IPR for pharmaceuticals: improving or impeding access?

The rationale for the protection of intellectual property rights (IPR) is the creation of incentives for technological innovation. However, IP protection may limit access to technologies and products because it creates monopolies and decreases competition in the market,

thereby allowing patent holders to set the prices. Neither can IPR protection (for example, as required under the TRIPS agreement), adequately address the interrelationship between incentives, IPR and innovation in pharmaceuticals. Patents on chemical compounds or molecules do not always necessarily result in priority disease drugs, or guarantee access to such drugs.

1. National regulatory agencies should contribute to ensuring the right balance between the need for innovation and equitable access, and between commercial and public health interests. To this end, they should closely collaborate with other ministries, the patent office and other national stakeholders in developing national patent legislation. However, regulatory agencies should not be involved in enforcement of patents as part of the process of regulatory decision making.

2. Countries should incorporate into their national legislation the relevant TRIPS flexibilities for export or supply of medicines of assured quality to countries with public health emergencies.

3. WHO should strengthen its capacity building to support countries in making maximum use of the TRIPS flexibilities.

The ICDRA Report and Recommendations are available on the WHO website at: http://www.who.int/medicines/icdra/en/index/html

Safety and Efficacy Issues

Tenofovir and nonsteroidal anti-inflammatories: acute renal failure

Canada — Tenofovir disoproxil fumarate (Viread®) is an antiretroviral indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in patients 18 years of age and older (1). Tenofovir was marketed on 15 March 2004. Nephrotoxicity, including renal failure, renal insufficiency, elevated creatinine level, hypophosphataemia and Fanconi syndrome, has been reported with the use of tenofovir in clinical practice, as indicated under warnings and precautions in the product monograph (1).

Health Canada has received 22 domestic reports of adverse reactions suspected of being associated with the use of tenofovir. Ten of these reports involved nephrotoxic reactions, three of which were observed when a nonsteroidal anti-inflammatory drug (NSAID) was added along with the antiretroviral therapy, which included tenofovir.

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion (1). Renal toxicity occurs with the accumulation of tenofovir in the proximal tubule and appears to be concentration dependent (2). Cases of renal failure with tenofovir have been reported in patients with no known risk factors (1). However, published case reports of nephrotoxicity suggest that there may be specific risk factors including pre-existing renal dysfunction, long duration of use, low body weight, concomitant use of drugs that may increase levels of tenofovir and other drug interactions (2–4). Long-standing HIV infection itself may lead to higher incidence of nephropathy (2).

Concurrent use of a nephrotoxic agent should be avoided with tenofovir, and the dosing interval should be adjusted in patients with a baseline creatinine clearance of less than 50 mL/min (1). NSAIDs are frequently used and are available over the counter. Since NSAIDs are potentially nephrotoxic, their use during tenofovir therapy may represent an additional risk for renal failure.

Extracted from the Canadian Adverse Reaction Newsletter. Volume 16, Issue 2, April 2006

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Update on status of contraceptive skin patch

Canada — The results of two studies looking at the risk of serious side effects when using the Ortho Evra® contraceptive patch marketed in the United States are currently being reviewed. The version of Evra® marketed in Canada is manufactured differently and contains less estrogen than the US product.

A preliminary report on one of the studies shows an approximately twofold increase in the risk of blood clots compared with users of an oral contraceptive. However, the second study concludes that the risk of non-fatal blood clots with the patch is similar to the risk of comparable oral contraceptives. Both studies, one of which is ongoing, were communicated to Health Canada by the manufacturer.

Blood clots are a relatively rare event but have been reported as a potential risk of all hormonal contraceptive therapy. Other serious side

effects being examined in the studies include heart attack and stroke. Once the review is complete, Health Canada will communicate any new safety information.

The current labelling information contains a description of the risks and a detailed section on the importance of discontinuing medication at the earliest sign of blood clots. Common symptoms for blood clots can include, but are not limited to, pain in the calf, shortness of breath, chest pain or coughing blood. Health Canada issued a previous statement regarding Evra on 28 November 2005.

Reference: Advisory 2006–14, 30 March 2006, available at: http://www.hc-sc.gc.ca

SSRI antidepressants linked to lung disorder in newborns

Canada — Generally, selective serotonin reuptake inhibitor (SSRI) treatment should only be continued during pregnancy if the benefits to the individual patient are thought to outweigh the risks to the unborn child, while also considering the benefits and risks of switching to another treatment option or stopping treatment altogether. SSRIs and other newer antidepressants prescribed for the treatment of depression include the following: bupropion, citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline and venlafaxine.

A study published recently in the *New England Journal of Medicine* suggests that use of SSRIs during the second half of pregnancy may be associated with a condition called persistent pulmonary hypertension of the newborn. Newborns with this rare but life-threatening condition do not receive enough oxygen in the blood and require intensive-care treatment to survive. According to the study, babies born with this condition were six times more likely than healthy babies to have been exposed to SSRIs. This information is considered to be preliminary at this time.

Numerous reports in Canada and abroad have already indicated that some children exposed to SSRIs and other newer antidepressants during pregnancy may develop serious complications at birth. An increase in the overall risk of major birth defects has also been associated with SSRI use.

Reference: Advisory 2006-11, 10 March 2006 available at: http://www.hc-sc.gc.ca

ACE inhibitors and birth defects

Use of angiotensin-converting–enzyme (ACE) inhibitors during the second and third trimesters of pregnancy is contraindicated because of their association with an increased risk of fetopathy. In contrast, first-trimester use of ACE inhibitors has not been linked to adverse fetal outcomes. The results of a study to assess the association between exposure to ACE inhibitors during the first trimester of pregnancy only and the risk of congenital malformations have recently been published in the *New England Journal of Medicine* (1, 2).

ACE inhibitors are among the most widely prescribed antihypertensive agents, but when used in the second half of pregnancy, they can cause oligohydramnios, fetal growth retardation, pulmonary hypoplasia, joint contractures, hypocalvaria and neonatal renal failure, hypotension and death. These effects result from the blockade of the conversion of angiotensin I to angiotensin II in the developing fetal kidneys.

A cohort of 29 507 infants born between 1985 and 2000 for whom there was no evidence of maternal diabetes were enrolled. In the first trimester alone, 209 infants with exposure to ACE inhibitors were identified, 202 infants with exposure to other antihypertensive medications in the first trimester, and 29 096 infants with no exposure to antihypertensive drugs at any time during gestation. Major congenital malformations were identified from linked vital records and hospitalization claims during the first year of life and confirmed by review of medical records.

Infants with only first-trimester exposure to ACE inhibitors had an increased risk of major congenital malformations as compared with infants who had no exposure to antihypertensive medications. In contrast, fetal exposure to other antihypertensive medications during only the first trimester did not confer an increased risk. Infants exposed to ACE inhibitors were at increased risk for malformations of the cardiovascular system and the central nervous system. It was concluded that exposure to ACE inhibitors during the first trimester cannot be considered safe and should be avoided.

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ACE inhibitors and pregnancy

United States of America — *The New England Journal of Medicine* (see above) has published an article reporting that infants whose mothers had taken an angiotensin-converting enzyme inhibitor (ACE inhibitor) during the first trimester of pregnancy had an increased risk of major congenital malformations, compared with infants who had not undergone first trimester exposure to ACE inhibitors. The number of cases of birth defects is small and the findings of this study have not yet been repeated (1).

According to the approved labels, ACE inhibitors are labelled as pregnancy category C for the first trimester of pregnancy and category D for the second and third trimesters. The existing prescribing information recommends discontinuing ACE inhibitors as soon as possible if a patient becomes pregnant. Because of the preliminary nature of the newly published data, the Food and Drug Administration (FDA) does not plan to change the pregnancy categories at this time (2), but healthcare professionals should take these findings into consideration with other information about a patient's medical situation during early pregnancy.

ACE inhibitors include: benazepril (Lotensin®), captopril (Capoten®), enalapril/enalaprilat (Vasotec® oral and injectable), fosinopril (Monopril®), lisinopril (Zestril® and Prinivil®), moexipril (Univasc®), perindopril (Aceon®), quinapril (Accupril®), ramipril (Altace®), and trandolapril (Mavik®)]

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2. http://www.fda.gov/cder/drug/infopage/ace_inhibitors/default.htm

Gadolinium–containing contrast agents and nephrogenic systemic fibrosis

United States of America — The Food and Drug Administration (FDA) is evaluating important safety information about gadolinium-containing contrast agents and a disease known as nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy (NSF/NFD) that occurs in patients with kidney failure. New reports have identified a possible link between NSF/NFD and exposure to gadolinium containing contrast agents used at high doses for a procedure called magnetic resonance angiography (MRA).

The FDA has learned of 25 cases of NSF/NFD in patients with kidney failure who received Omniscan®, a gadolinium-containing contrast agent following an MRA. The FDA is actively investigating whether exposure to a gadolinium-containing contrast agent for MRA is associated with the development of NSF/NFD. In the meantime, the following recommendations are being provided.

Gadolinium-containing contrast agents, especially at high doses, should be used only if clearly necessary in patients with advanced kidney failure. It may be prudent to institute prompt dialysis in patients with advanced kidney dysfunction who receive a gadolinium contrast MRA.

Five gadolinium-containing contrast agents are FDA-approved for use during magnetic resonance imaging (MRI): Omniscan®, OptiMARK®, Magnevist®, ProHance®, and MultiHance®. None of these drugs are FDA approved for MRA. The dose of gadolinium-containing contrast agent given to patients undergoing an MRA test is often higher (up to three times) than the approved dose for MRI.

NSF/NFD appears to occur in patients with kidney failure along with acidosis. Patients with NSF/NFD have tight and rigid skin making it difficult to bend joints. NSF/NFD may also result in fibrosis, or scarring, of body organs resulting in the inability of body organs to work properly and can lead to death. Scientists first identified NSF/NFD in 1997 and the cause of NSF/NFD is unknown. Worldwide, there are approximately 200 reports of NSF/NFD.

The 25 cases of NSF/NFD were reported in May 2006, by the Danish Medicines Agency. Among these, 20 cases occurred in Denmark and five cases occurred in Austria. The patients developed NSF/SFD within 3 months after receiving the gadolinium-containing contrast agent (2).

The FDA is gathering additional information about NSF/NFD and investigating whether other patients who received gadolinium-containing contrast agents developed NSF/NFD.

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Gatifloxacin and blood glucose disturbances

Singapore — The Health Sciences Agency (HSA) would like to draw the attention of healthcare professionals to the known adverse effects of hypoglycaemia and hyperglycaemia associated with gatifloxacin (Tequin®), a fluoroquinolone antibiotic, and the recent contraindication on the use of the drug in patients with diabetes mellitus.

Serious cases of both hypoglycaemia and hyperglycaemia have been reported with gatifloxacin during post-marketing surveillance. From the overseas spontaneous postmarketing reports, it was noted that cases of blood glucose disturbances usually occurred in diabetic patients. There were very rare events of hypoglycaemia and hyperglycaemia which were life-threatening. In the majority of cases, the patients had other underlying medical problems and were receiving concomitant medications that may have contributed to the glucose abnormality. A few of these cases resulted in fatalities.

The patients particularly at risk include diabetics and the elderly (>75 years of age) who may have unrecognized diabetes, age-related decrease in renal function, underlying medical problems, and/or are taking concomitant medications associated with dysglycaemia. However, dysglycaemia has been reported to occur in patients without a history of diabetes.

Gatifloxacin has been demonstrated to be associated with transient disturbances in glucose homeostasis, including an increase in serum insulin and decrease in serum glucose following administration of initial doses. This is sometimes associated with symptomatic hypoglycaemia. In addition, increases in fasting serum glucose were observed, usually after the third day of gatifloxacin administration and continuing throughout the duration of treatment. The levels return to pre-dose values by 14 days after the completion of treatment.

To ensure the safe and effective use of gatifloxacin, the company is recommending a contraindication in patients with diabetes mellitus. Physicians are advised to closely monitor the blood glucose of nondiabetic patients who are at risk of dysglycaemic events for signs and symptoms of blood glucose disturbances. Risk factors include older age, renal insufficiency, drug interactions with glucose-altering medications (such as antidiabetic agents like glibenclamide). If signs and symptoms of either hypoglycaemia or hyperglycaemia occur in any patient treated with gatifloxacin, appropriate therapy should be initiated immediately and gatifloxacin should be discontinued.

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Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious and unexpected adverse drug reactions. A signal is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information". All signals must be validated before any regulatory decision can be made.

Essential Medicines

WHO Model List of Essential Medicines and developed countries: a comparison with the Lothian Joint Formulary

Essential medicines lists and formularies are valuable public health tools which balance consideration of need, efficacy, safety and cost. The WHO Model List of Essential Medicines has been widely adopted or adapted in over 150 countries, and it has been suggested that industrialized countries should incorporate the Essential Medicines concept into their health policy. This summary describes a comparative study* conducted to investigate whether the WHO Model List of Essential Medicines is suitable as a basis for generating or reviewing a formulary in the industrialized world. It builds on a critical analysis of the WHO Model List of Essential Medicines and the Scottish Lothian Joint Formulary and determines, in particular, the relevance of the List for developed countries.

Essential medicines concept and the WHO Model List

There is great disparity between the health care expenditure of developing and industrialized countries. In high-income countries, medicines account for less than 15% of overall health care expenditure compared with 25–70% in developing countries (1). It was within this climate that the concept of essential medicines was introduced in 1977 with the publication of the first WHO Model List of Essential Medicines (EML) (2).

Essential medicines are defined as "those that satisfy the priority health needs of the population." It is a national responsibility to identify which medicines are "essential", with selection dependent on disease prevalence, evidence of efficacy and safety, and comparative cost-effectiveness. Essential medicines should be affordable, of assured quality, and available at all times within functioning health systems in adequate amounts and appropriate dosage forms. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations.

The EML is composed of a core list and a complementary list (3). The core list is "a list of minimum medicine requirements for a basic health care system." It contains the most efficacious, safe and cost-effective medicines for priority diseases, which are based on current and predicted public health relevance, with potential for safe and cost-effective treatment. The complementary list contains "essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed."

In the EML, a square box symbol indicates that there are many possible medicines within a specific therapeutic class that can be used to treat a given condition (2, 4). This symbol was introduced in recognition of the global variation that can occur in the availability and cost of medicines. A medicine included in the EML is the one of that class for which there is the best evidence for effectiveness and safety. It may be the first to be marketed, or a safer or more effective newer medicine. Alternatively, if there is no difference in efficacy and safety, the least expensive medicine.

** Article based on "A comparison of the WHO Model List of essential medicines and the Lothian Joint Formulary", a study conducted by Ms Sharon Hems, Lothian Joint Formulary Pharmacist, St John's Hospital, Livingston, Scotland (available from Sharon.Hems@isd.csa.scot.nhs.uk) and Dr Richard Laing, Department of Medicines Policy and Standards, World Health Organization, Geneva*

Role of formularies

The essential medicines process is comparable to many systems adopted by industrialized countries to develop formularies. Formularies are restricted lists of medicines from which appropriate therapy can be selected, and are aimed to encourage safe, appropriate and cost–effective prescribing. Information regarding doses, indications, adverse effects, contraindications and warnings for medicines in the EML is contained in the WHO Model Formulary (5). The WHO Model Formulary does not provide information on comparative costs or additional medicines.

The Lothian Joint Formulary (LJF) (7) was first produced in 2001 to serve a population in the Edinburgh area of 770 000, with 530 General Practitioners in 130 practices, 140 community pharmacies, two large teaching hospitals, one paediatric hospital and one district general hospital. Annual medicines expenditure in primary care is currently in excess of £120 million.

The LJF is intended to be used in conjunction with the British National Formulary (BNF) (6), which provides further information on side-effects, drug interactions, costs, and more comprehensive information on a wider range of medicines.

The WHO Expert Committee on the Selection and Use of Essential Medicines has developed a transparent submission and review web-based process. If the data produced in this process could also be used by the Lothian Formulary Committee, this could improve the efficiency of the selection process. If the EML process is suitable as a basis for generating or reviewing a formulary in the industrialized world, this could benefit both members of the WHO Expert Committee and formulary committees (8, 9).

The selection of medicines for inclusion in the EML or the LJF will depend on disease burden, and evidence of efficacy, safety and comparative cost-effectiveness. If appropriate, drug stability, the need for special diagnostic or treatment facilities, and pharmacokinetic properties may also be considered. The EML is intended as a starting point for national governments and institutions to develop their own formularies and a number of factors may be taken into account when they adapt the EML, such as:

- local demography and pattern of diseases;
- training and experience of available personnel;
- local availability of medicines;
- financial resources; and
- environmental factors.

In Lothian, formulary working groups have used historical prescribing patterns to provide an insight into how drugs were used locally and highlight prescribing areas of concern. Additional factors considered by the Lothian Formulary Committee are the patent status of the medicine, and information on anticipated use and overall cost. Recommendations produced by the Scottish Medicines Consortium (SMC) will influence the inclusion of newly licensed medicines, and new formulations or indications. However, the Committee will also consider applications for unlicensed medicines or medicines used outside their licensed indications. In addition, there is a process in place for appeal against decisions.

In contrast to the EML, the LJF specifies first and second choice medicines for the treatment of common conditions occurring in primary and secondary care and it therefore does not contain many medicines for the treatment of poisoning, nor sections on blood products, immunologicals or peritoneal dialysis, as in the EML. The LJF aims to cover approximately 80% of prescribing situations, and includes dosing information and prescribing notes to highlight key messages regarding the medicines or conditions being treated (7).

The majority of medicines contained in the LJF and the EML are single compounds. Combination products may be selected if they have a proven advantage in therapeutic effect, safety or adherence compared to the individual compounds administered separately. For example, the WHO Expert Committee encourages the use of fixed-dose combination products for the treatment of HIV/AIDS, tuberculosis and malaria to decrease the emergence of drug resistance (3).

Differences between the EML and LJF

The LJF provides guidance on commonly occurring disorders in Lothian, which will differ from those in developing countries. For

instance, the leading causes of death and morbidity in Africa, Asia and South America are HIV/AIDS, tuberculosis, malaria and respiratory infections (10, 11). This is reflected in the choice of medicines in the EML, which contains substantially more medicines (107) for the treatment of infections than the LJF (31). Infectious diseases are also the most common cause of death worldwide, followed by cardiovascular diseases, maternal and perinatal conditions, respiratory infections and cancers (1). Within the UK, however, circulatory diseases (including heart disease and stroke) and cancer are the two most common causes of death (12).

Another factor that influences the choice of medicines is the age distribution of the population. In some African countries, average life expectancy has dropped below 40 due to HIV/AIDS (13). Almost 20% of global deaths in 2002 were children aged less than 5 years of which 98% occurred in developing countries (12). The main causes are infectious and parasitic diseases partly as a result of the HIV/AIDS epidemic.

It is also reported that more than 60% of deaths in developed countries occur beyond age 70, compared with about 30% in developing countries (12). Diseases which occur predominantly in older people, such as osteoarthritis, dementia, ischaemic heart disease and cerebrovascular disease, will therefore be observed more frequently in the United Kingdom than in developing countries. In addition, the LJF contains medicines for the treatment of lifestyle illnesses such as smoking or obesity. It would be expected that patient demand and expectation, which can influence prescribing of medicines for these conditions in developed countries, would be different in developing countries. However, there are sections within the LJF which may be appropriate for inclusion in the EML such as ear, nose and throat (ENT), oral nutrition and genito-urinary disorders.

In Scotland, it has been estimated that substituting premium-priced products with cheaper standard alternatives could result in a potential saving of £5.8 million (14). The contrast in the number of formulations may also suggest that the range of formulations in the EML should be revised, in particular for paediatric formulations (25).

The LJF has an advantage in being a dynamic document which is continually revised and updated to reflect evidence-based medicine as well as local expertise and practice. Since the EML is updated every 2 years there is a risk that some recommendations could be out of date. An electronic consultative mechanism

Table 1: Content of the EML and the LJF

Content	EML	LJF
Total number of medicines (including duplicate entries)	369	531
Number of medicines by name only (not including duplicate entries)	311	417
Number of medicines common to EML and LJF (by medicine name only, excluding duplicates)	45% (139) of medicines in EML are in LJF	33% (139) of medicines in LJF are in EML
Number of medicines common to EML and LJF (considering section, including duplicates)	41% (153)	29% (153)
Number of formulations (including duplicates)	622	1412
Average number of formulations per medicine	1.7	2.7
Number of medicines with a square box	25 %	N/A

is needed to cope with such eventualities, and to enable changes to be made to the EML more rapidly.

One of the major advantages of the WHO Expert Committee is the transparency of its decision-making processes. This makes it possible to identify the rationale behind the addition or removal of medicines from the EML, and therefore help facilitate local decisions with regard to this advice. However, there has been concern regarding the implementation of recommendations. For example, magnesium sulphate was added to the EML in 1997 for the treatment of eclampsia and pre-eclampsia. Despite this, however, it is still not available in many low and middle-income countries, and clinical guidelines have been poorly implemented (16, 17). An implementation strategy, including promotion of formulary recommendations and provision of feedback to prescribers on formulary adherence, has been developed in Lothian to increase awareness and use of the LJF, and a similar approach may benefit WHO.

Proposals for action

This study revealed interesting differences in the processes and products of the EML and the LJF. The decision-making processes of the two committees are similar but the WHO Expert Committee benefits from a more transparent and clearly documented process. There would be advantages, however, in reviewing the EML

Table 2: Number of medicines in each section of the EML and the LJF

Section	No. in EML	No. in LJF	No. in both EML & LJF (%)
1. Anaesthetics	13	21	53
2. Analgesics, DMARDs	11	30	39
3. Antiallergics, anaphylaxis	5	7	83
4. Poisoning	14	4	11
5. Antiepileptics	7	12	53
6. Infection	107	31	27
7. Migraine	3	12	40
8. Cancer, palliative care	26	59	45
9. Parkinsons	2	9	18
10. Blood	8	16	50
11. Blood prods	3	-	-
12. CVS	25	49	43
13. Skin	21	53	27
14. Diagnostic	8	2	40
15. Disinfectants	6	3	44
16. Diuretics	5	5	60
17. GI	11	29	30
18. Endocrine	19	59	33
19. Immunologicals	20	-	-
20. Muscle relaxants, cholinesterase inhibitors	5	9	57
21. Eye	10	26	33
22. Oxytocics, antioxytocics	6	1	0
23. Peritoneal dialysis	1	-	-
24. Psychotherapeutic medicines	10	37	34
25. Respiratory	4	19	26
26. Electrolyte	9	4	31
27. Vitamins and minerals	10	8	22
28. ENT	-	13	-
29. Oral nutrition	-	1	-
30. Genitourinary disorders	-	12	-
Total	**369**	**531**	**17%**

more frequently and introducing an implementation strategy similar to that developed in Lothian.

Some important points for consideration

- The decision-making processes of Drug and Therapeutics or Formulary Committees should be transparent and clearly documented.
- Frequent review and an implementation strategy are necessary to ensure that formularies are up to date and used in practice.
- When the WHO Model List of Essential Medicines is published every two years, formulary committees could compare their list with the EML according to the methods described in this study.
- The WHO Model List of Essential Medicines is a useful tool for the review of a formulary but is not suitable for adoption, without adaptation, within the industrialised world.
- The WHO electronic library is a useful resource and the decisions of the WHO Expert Committee should be considered by Drug and Therapeutics or Formulary Committees.

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Adherence to WHO's Model List of Essential Medicines in two European countries

The concept of Essential Medicines is one of the most important tools available for improving public health in developing countries and key elements include the WHO Model List of Essential Medicines (1, 2). It has been proposed that developed countries could also make use of the Model List to a greater extent, in particular to promote better quality of care and control drug expenditure (2). However, the applicability of the Essential Medicines concept for industrialized countries has been questioned and there is a lack of studies analysing the use of the Model List in this context (3).

In this article, adherence to the 2003 WHO Model List of Essential Medicines (EML) was analysed through an observational study of medicines use in outpatient care in two European countries — Croatia and Sweden. Data on dispensed prescriptions and over-the-counter (OTC) drugs were collected from wholesalers in Croatia and pharmacies in Sweden. WHO Collaborating Centres in Norway and Sweden have developed and apply several methodologies to evaluate drug use and quality of drug utilization patterns. In the study, analyses focused on medicines accounting for 90% of use in Defined Daily Doses (DU90%). DU90% profiles provide a quick method to overview and evaluate potential for improvement while offering a reflection on the relevance and appropriateness of the WHO Model List of Essential Medicines.

Drug use and utilization: new challenges for the WHO Model List of Essential Medicines

The WHO Model List of Essential Medicines (EML) includes about 300 drugs intended to provide safe and effective treatment for the majority of diseases (4). The selection of medicines is based on disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness: basically the same principles that have been applied by Drug and Therapeutics Committees for many years (5).

The medicines included in the EML are intended to be available at all times in adequate amounts, in appropriate dosage forms, with assured quality, and at a price the individual and the community can afford (3). The EML is useful both from a medical and an economical point of view as a tool for information, prescriber training and medical audit as well as to simplify procurement, drug distribution and reimbursement (2).

Rational drug use has been defined as the act of patients receiving medication appropriate to their medical needs, in doses meeting their own individual requirements, for an adequate period of time and at the lowest costs to them and to the community (6). A number of indicators have been recommended by the WHO to assess the extent of inappropriate drug use in a practice, a region or a country (7). Although crude, these indicators are easily monitored and may be used to identify particular drug-use issues that may need more detailed examination.

WHO indicators to quantify the impact of an essential drugs programme include the percentage of drugs prescribed from the EML or a formulary. However, this indicator does not take into account the volume of drugs used, and is not based on the internationally accepted measurement unit of utilization, the Defined Daily Dose (DDD) (8).

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The Drug Utilization 90% (DU90%) method describes patterns of drug utilization. It was originally developed with the aim to make aggregated drug statistics on dispensed drugs useful for quality assessment (8–10). DU90% is a further development of a "top 10" list providing both quantitative and qualitative data. The focus is on the drugs that account for 90% of the volume and adherence to guidelines within this 90% (8–10). The DU90% method has proven to be useful both for international comparisons of drug utilization and feedback to doctors on prescribing patterns (10–16). It can be applied with aggregated data easily available in healthcare systems. The DU90% method can also be considered as a further development of the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) methodology, recommended by WHO as a common language for describing the use of drugs — therapeutic intensity — in a population (8,17).

The study evaluated the feasibility of using the DU90%-method to assess the quality of drug use in two European countries using the 2003 EML as a reference (4).

Methods

The overall quality of outpatient drug use was evaluated in Croatia and Sweden, two European countries with comparable access to drug utilization data but with substantial differences in GDP and pharmaceutical markets, e.g., different number of drugs available and different healthcare organization. Basic facts about the countries are presented in Table 1.

Data on dispensed prescription and OTC drugs were collected for the year 2003. The Croatian data were captured from the wholesalers, while the Swedish data were obtained from prescriptions and OTC sales from the National Corporation of Pharmacies which has the sole and exclusive right to retail medicines to the general public and to hospitals.

Drug use was expressed in Defined Daily Doses (DDDs) and expenditure in Euros. Total drug consumption was measured using DDDs per 1000 inhabitants daily (DDD/TID). A number of drugs (231 in Croatia and 359 in Sweden) did not have assigned DDDs and therefore had to be excluded. These included dermatological preparations, nasal solutions, ophthalmic drops, cytotoxics, vaccines and some combination products.

Patterns of drug use were analysed focusing on medicines accounting for 90% of use (DU90%) in DDDs and, within this segment, adherence to the 13th WHO Model List of Essential Medicines issued in 2003 (4). The core list presents a minimum medicine need for a basic health care system listing the most efficacious, safe and cost-effective medicines for priority conditions. The complementary list presents essential medicines for priority diseases, for which specialized diagnostic/monitoring and medical care/training are needed. Medicines marked with a square symbol are those with similar clinical performance within a pharmacological class ("me-too" drugs). Both the core and complementary list with 316 drugs were used for this analysis.

DU90% profiles were analysed for all drugs (ATC A–V) and for the seven ATC pharmacological groups with high utilization, reflecting major disease patterns in the two countries Tables 2 and 3.

Table 1. Facts about Croatia and Sweden 2002 (18)

Statistics	Croatia	Sweden
Population	4.4 million	8.9 million
Percentage of population aged 60+	21.7 %	23.2 %
GDP per capita	$8,636.-	$27,271.-
Health expenditure per capita	$630.-	$2,512.-
Health expenditure % of GDP	7.3 %	9.3 %

Table 2. Drug utilization within selected therapeutic areas: Croatia and Sweden

ATC	Pharmacological group	Croatia					Sweden				
		DDD/TID	Number of Drugs Tot.	DU90%	Adherence 1*	2*	DDD/TID	Number of Drugs Tot.	DU90%	Adherence 1*	2*
A02	Drugs: acid related disorders	15	9	4	62%	62%	40	15	6	12%	12%
A10	Antidiabetic drugs	34	11	7	77%	77%	42	18	10	73%	73%
C	Cardiovascular drugs	214	52	19	31%	76%	351	103	25	36%	70%
J01	Antibiotics	19	33	7	78%	78%	15	58	13	64%	72%
M01A	NSAIDs	41	10	4	15%	15%	51	23	7	34%	34%
N06A	Antidepressants	10	10	5	8%	19%	62	21	7	4%	4%
R	Respiratory drugs	45	30	12	21%	32%	135	71	26	10%	27%

1 = Adherence to the core list within DU90%.*
2 = Adherence within DU90% including alternatives to drugs marked with a square symbol in the EML.*

Table 3. Most used drugs in Croatia and Sweden in percent of total use within each pharmacological group. Utilization in DDDs.

ATC	Pharmacological group	Croatia	Sweden
A02	Drugs for acid related disorders	*Ranitidine (46%)* Pantoprazole (20%) Omeprazole (14%) *Aluminium hydroxide (10%)*	Lansoprazole (29%) Omeprazole (26%) Esomeprazole (16%) *Ranitidine (11%)*
A10	Antidiabetic drugs	*Glibenclamide (35%)* *Insulin (human), fast-acting (20%)* *Metformin (14%)* ■ Gliclazide (7%)	*Metformin (22%)* *Insulin (human), intermediate (16%)* *Glibenclamide (14%)* *Insulin (human), combined (9%)*
C	Cardiovascular drugs	■ Lisinopril (13%) ■ Amlodipine (11%) *Furosemide (10%)* *Atenolol (7%)*	*Furosemide (14%)* Simvastatin (10%) *Enalapril (6%)* ■ Ramipril (6%)
J01	Antibiotics	*Amoxicillin + klavulanic acid (28%)* *Amoxicillin (25%)* Cefalexin (10%) *Doxycycline (9%)*	*Phenoxymethylpenicillin (28%)* *Doxycycline (12%)* Methenamine (11%) ■ Flucloxacillin (8%)
M01A	NSAIDs	Diclofenac (55%) *Ibuprofen (14%)* Piroxicam (13%) Ketoprofen (10%)	*Ibuprofen (31%)* Diclofenac (17%) Naproxen (16%) Celecoxib (8%)
N06A	Antidepressants	Paroxetine (29%) Fluoxetine (24%) Sertraline (19%) ■ Maprotiline (11%)	Citalopram (33%) Sertralin (24%) Venlafaxine (9%) Mirtazapine (8%)
R	Respiratory drugs	Loratadine (17%) *Salbutamol (12%)* Oxymetazoline (12%) Naphazoline (11%)	Budesonide (9%) Oxymetazoline (8%) Xylometazoline (8%) ■ Terbutaline (7%)

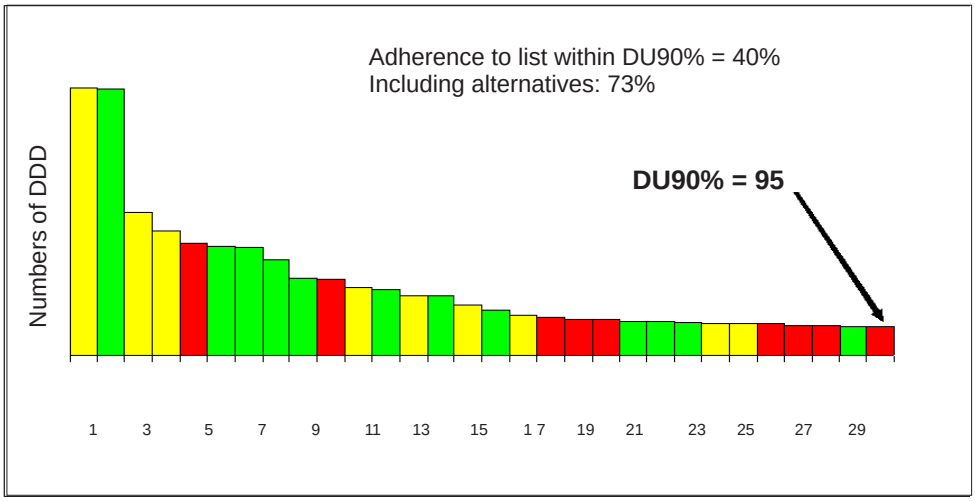
Italic = Included in Model list of Essential Medicines (EML). ■ *= Alternative drugs, marked with a square symbol in EML.*

Results

Total utilization was 682 DDD/TID in Croatia compared to 1360 in Sweden. In Croatia 95 substances (24% of 388) accounted for 90% of use compared to 174 (21% of 828) in Sweden. Drug profiles had many similarities in the two countries with high use of drugs for treatment of cardiovascular disease, diabetes, pain and psychiatric disorders. (Figures 1A and 1B).

Adherence to the EML within DU90% was 40% in Croatia and 37% in Sweden. Low adherence in both countries was partly due to the utilization of “me-too” drugs different to those included in the EML. When adding the medicines suggested as alternatives to those recommended in the EML (square symbols), adherence increased to 73% and 53%, respectively. There were also some drugs extensively used in both countries that were not included in the EML (e.g. proton pump inhibitors (PPIs), serotonin selective reuptake

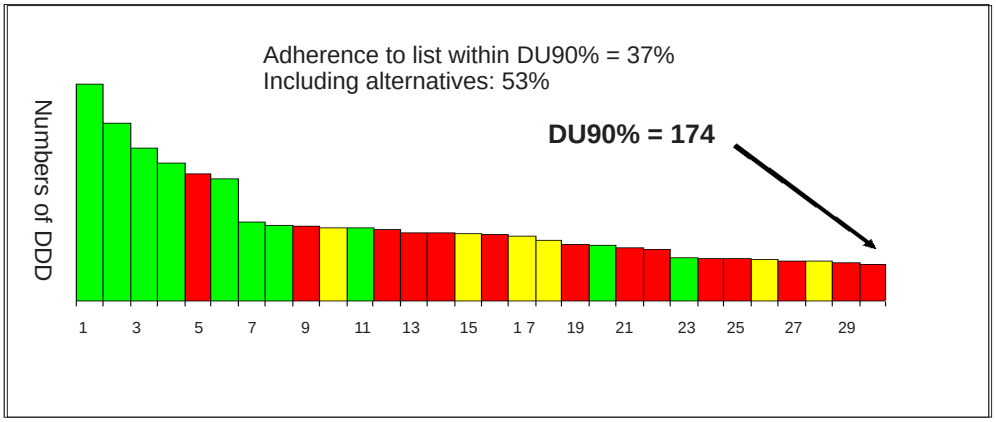
Figure 1A. DU90% profile for Croatia 2003 — outpatient care



Green = medicines included in the core EML. Yellow = alternatives to medicines, i.e. those marked with a box symbol in the EML. Red = medicines not on the EML.

	SUBSTANCE	(DDD)	Mill. DDD	% TOT	Mill Euro	Euro/DDD
1	Estradiol	2 mg	85	7.7%	1.1	0.01
2	Acetylsalicylic acid	1 tabl	84	7.7%	2.3	0.03
3	Lisinopril	10 mg	45	4.1%	12.3	0.27
4	Amlodipine	5 mg	39	3.6%	10.0	0.25
5	Diclofenac	0.1 g	36	3.3%	6.6	0.19
6	Ascorbic acid (vit C)	0.2 g	35	3.2%	1.1	0.03
7	Furosemide	40 mg	34	3.1%	1.6	0.05
8	Diazepam	10 mg	31	2.8%	3.0	0.10
9	Atenolol	75 mg	25	2.3%	3.5	0.14
10	Simvastatin	15 mg	24	2.2%	16.2	0.67
11	Isosorbide mononitrate	40 mg	22	2.0%	4.0	0.19
12	Levothyroxine	0.15 mg	21	1.9%	0.4	0.02
13	Oxazepam	50 mg	19	1.7%	4.4	0.23
14	Glibenclamide	7 mg	19	1.7%	1.8	0.09
15	Alprazolam	1 mg	16	1.5%	2.5	0.16
16	Verapamil	0.24 g	15	1.3%	2.5	0.17
17	Cilazapril	2.5 mg	13	1.2%	4.3	0.34
18	Loratadine	10 mg	12	1.1%	3.3	0.27
19	Metildigoxin	0.2 mg	11	1.0%	0.9	0.08
20	Chlortalidone	25 mg	11	1.0%	0.8	0.07
...						
95						
DU90%	1-95		987	90.1%	241	0.24
	96-388		109	9.9%	93	0.85
TOTAL	1-388		1096	100.0%	334	0.30

Figure 1B. DU90% profile for Sweden 2003 – outpatient care



Green = medicines included in the core EML. Yellow = alternatives to medicines, i.e. those marked with a box symbol in the EML. Red = medicines not on the EML.

	SUBSTANCE	(DDD)	Mill. DDD	% TOT	Mill Euro	Euro/DDD
1	Acetylsalicylic acid	1 tablet	201	4.6%	10	0.05
2	Furosemide	40 mg	164	3.7%	14	0.08
3	Sodium fluoride	1.1 mg	142	3.2%	11	0.07
4	Ascorbic acid (vit C)	0.2 g	128	2.9%	3	0.02
5	Simvastatin	15 mg	118	2.7%	52	0.44
6	Paracetamol	3 g	113	2.6%	49	0.43
7	Enalapril	10 mg	73	1.7%	10	0.13
8	Levothyroxine	0.15 mg	71	1.6%	9	0.12
9	Lactulose	6.7 g	70	1.6%	8	0.11
10	Ramipril	2.5 mg	68	1.5%	22	0.32
11	Atenolol	75 mg	68	1.5%	9	0.13
12	Citalopram	20 mg	67	1.5%	27	0.41
13	Atorvastatin	10 mg	64	1.4%	45	0.71
14	Cyanocobalamin	1 mg	63	1.4%	8	2.00
15	Metoprolol	0.15 g	63	1.4%	39	0.63
16	Multivitamins and iron	1 tablet	62	1.4%	4	0.06
17	Felodipine	5 mg	60	1.4%	23	0.37
18	Isosorbide mononitrate	40 mg	57	1.3%	9	0.15
19	vitamin b-mixed	1 tablet	53	1.2%	9	0.16
20	Ibuprofen	1.2 g	51	1.2%	21	0.42
...						
174						
DU90%	1-174		3,970	90.1%	1,535	0.39
	175-828		438	9.9%	961	2.19
TOTAL	1-828		4,408	100.0%	2,496	0.57

inhibitors (SSRIs) and statins). Including them, adherence would have been 78% in Croatia and 64% in Sweden.

There were substantial differences between the two countries in the total utilization (DDD/TID), the range of drugs and adherence within the selected therapeutic areas (Tables 2 and 3).

Discussion

Drug utilization was twice as high in Sweden as in Croatia. In addition, different drugs were used in Sweden than in Croatia, both totally and in the selected therapeutic areas (Table 3). These cannot be explained by differences in morbidity but rather by differences in GNP per capita and therapeutic traditions. It has been suggested that high-quality prescribing is

associated with the use of a relatively limited number of evidence-based documented pharmaceutical products (19). The relationship between the range of drugs and quality has been demonstrated for individual prescribers (20). It is not obvious what impact the range of different drugs prescribed in a region or a country may have on public health. A reasonable distribution among the major ATC groups can be expected. A lack of products in certain ATC categories, as well as too many products in other categories, may indicate quality problems. The high number of "me-too" drugs used in Sweden is probably explained by the higher GNP/capita and through EU membership increasing the availability of drugs on the market.

How many medicines cover the needs of a population? In our study, 95 substances (of 388) accounted for 90% of outpatient use in Croatia compared with 174 (of 828) in Sweden. The Essential Medicines List includes 316 drugs. However, the selection of medicines reflects the global need, including drugs for hospital care and many drugs for the treatment of infectious diseases not prevalent in a European population.

Low adherence to the EML in both countries was mainly explained by the use of "me-too" drugs and newer drugs not included in the 2003 EML (PPIs, SSRIs and statins). These medicines were highly used in both countries. It has been shown that they offer advantages over older therapies (21–24). The study therefore also raises questions concerning the relevance of the WHO EML. It seems that the EML may be more relevant for developing countries where the overall adherence is reported to be much higher. Although different methods (prescription audits) were used, adherence to WHO EML in Jordan primary care was reported to be 93% (25), while similar studies from Bangladesh, Nepal and Tanzania reported 85% and 88% (7). However, the absence of PPI's, SSRI's and statins reflect a serious problem in the comprehensive nature of the WHO EML. These products are widely used in developed countries.

Comparison of the profiles for the selected pharmacological groups revealed interesting differences between the two countries (Table 2). Utilization of drugs for acid related disorders was almost three times higher in Sweden than Croatia. The three most used drugs for acid related disorders in Sweden were all proton pump inhibitors (PPIs) while ranitidine was the most used drug followed by two PPIs in Croatia. Half of the PPI volume in Sweden was prescribed to patients with unspecific dyspepsia: which is not according to treatment guidelines (26).

The overall utilization and adherence in diabetic treatment was similar. However, metformin was used to a greater extent in Sweden, which is in accordance with findings from the UK Prospective Diabetes Study that metformin decreases mortality and morbidity (27).

Low adherence for cardiovascular drugs in both countries was mainly explained by a high utilization of "me-too" drugs. Some examples were lisinopril, ramipril and amlodipine instead of the EML drugs enalapril and nifedipine. Adherence rose substantially when including alternatives to medicines marked with a square symbol.

No statin is included in the EML. However, it is stated in the EML that since no single drug has been shown to be significantly more effective or less expensive, the choice of drug should be decided on a national level (28). Simvastatin is well documented, and it had a lower price than other statins in both countries due to an expired patent at the time of the study. It should therefore be considered as the drug of choice to be included on the EML.

As reported for other European countries, there were striking differences in the utilization of antibiotics (29). It was the only therapeutic area where utilization was higher in Croatia than in Sweden. The most commonly used antibiotic in Croatia was amoxicillin in fixed combination with clavulanic acid. Although included in the EML, it is not a first choice medicine for the empiric treatment of upper respiratory tract infections, the most commonly treated (often viral!) infections in primary care. The most used antibiotic in Sweden was phenoxymethylpenicillin, a more reasonable choice with regard to the development of resistance and price. In Croatia, antibiotics were the drug group with the highest adherence to the EML — which does not imply that they are the most rationally used drug group.

Total utilization of NSAIDs was similar, but the range of medicines differed between countries. Overall utilization had increased but the choice of drugs was similar to that observed in 2000 (12). The two most extensively used drugs were ibuprofen and diclofenac in both countries. Questions could be raised about the high use of piroxicam in Croatia and coxibs in Sweden. Ibuprofen was the only NSAID included in the EML. It could be worth adding diclofenac to the EML since it is at least as effective as ibuprofen and has a similar safety profile (30).

Utilization of antidepressants was six times higher in Sweden. This might reflect a higher prevalence of depression, differences in access to healthcare or differences in treatment practices. Most used antidepressants in both countries were SSRIs, but the newer SNRIs, venlafaxine and mirtazipine were only used in Sweden. We propose that an SSRI is added to the WHO Model list since these drugs appear to have fewer side effects than tricyclic antidepressants (23).

The low adherence for respiratory drugs in both countries was mainly explained by the use of newer, less sedating antihistamines instead of chlorphenamine and high use of budesonide, fluticasone and terbutaline instead of the recommended beclometasone and salbutamol, respectively. There was also a high use of nasal decongestants and cough suppressants in both countries. There were no alternative drugs to those included in the WHO Model List.

A new version of the EML has been issued since this study was performed (31). Some newer drugs have been included though not a PPI, an SSRI or a specific statin. However, to make the list more relevant, we propose that at least the complementary list includes a statin, a PPI, a SSRI, a new nonsedating antihistamine and diclofenac. We also suggest that a revision of the square symbols should be undertaken. Results from both countries have shown that the EML, if it included suggested drugs, would be closer to its initial mission of covering the necessary treatment options for the majority of the world's population.

In an ideal world, "rationality" should be determined by looking at patient outcomes, i.e. does the treatment succeed in reducing morbidity and mortality and increasing patient quality of life. However, it is seldom possible to analyse patient outcome with routinely available data, and the outcome is only partially influenced by the processes controlled by healthcare professionals. Therefore, process-oriented quality indicators are used to monitor the performance of healthcare systems.

The advantage of DU90% compared to the drug-use indicators recommended by WHO is that it takes into account the volume of used drugs, utilizes easily collectible data and is based the ATC–DDD methodology that facilitates international comparisons. This study has confirmed that the DU90% method is simple, inexpensive, understandable and easy to use for quality assessment. Comparison with the EML may be useful for decision-making (e.g., preparing national formularies). The DU90% profiles provide a quick overview of potential improvements in both studied countries but are also a reflection on the relevance and appropriateness of the WHO Essential Medicines List.

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Regulatory Action and News

Transgenic antithrombin alfa approved

European Union — The European Medicines Agency (EMEA) has adopted the first positive opinion for a medicinal product derived from transgenic biotechnology. ATryn®, contains antithrombin alfa, a recombinant-DNA human anti-clotting blood protein. Antithrombin alfa is extracted from the milk of goats which have the human antithrombin gene inserted, and that enables them to produce the human protein in their milk.

The Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that ATryn® should be authorized for use in patients with congenital antithrombin (AT) deficiency (inherited reduction of antithrombin) undergoing surgery, for the prophylaxis of deep-vein thrombosis and thromboembolism.

In February 2006, ATryn® received a negative opinion. At the request of the company, the Committee started a procedure to re-examine its opinion, as part of which further expert advice was obtained. The CHMP has concluded that the benefits of ATryn® outweigh its risks, and subsequently adopted a final positive opinion recommending that ATryn® be granted a marketing authorization.

Reference: European Medicines Agency. Press Release, 2 June 2006, Doc. Ref. EMEA/203163/2006 at: www.emea.eu.int

EMEA Management Board moves for greater transparency

European Union — Transparency was the main topic for discussion of the European Medicines Agency's Management Board at its 8 June 2006 meeting. The Board agreed in principle to publish its meeting agendas and minutes, together with all non-confidential documents it adopts. Details will be set out in a policy document to be presented at the next Board meeting on 28 September 2006.

The Board also adopted revised rules on access to EMEA documents. Following this revision, the Agency's rules better reflect European Union legislation on access to documents, and the types of documents that can be released have been clarified. The rules also introduce the possibility for the Agency to give partial access to documents when exceptions to release apply to other parts of the document.

Reference: European Medicines Agency. Press Release, 12 June 2006 at: www.emea.eu.int

Bupropion approved for seasonal depression

United States of America — The Food and Drug Administration (FDA) today approved bupropion HCL extended release tablets (Wellbutrin XL®) for prevention of major depressive episodes in patients with a history of seasonal affective disorder (SAD). This is the first drug approved for SAD. Bupropion has been approved for treatment of major depressive disorder.

SAD is characterized by recurrent major depressive episodes that usually coincide with the seasonal decrease of daylight during autumn and winter. Depressive episodes can last up to 6 months. Although patients with SAD may have depressive episodes during other times of the year, the diagnosis of seasonal affective disorder requires that the number of seasonal episodes substantially outnumber the non-seasonal episodes during the individual's lifetime.

A major depressive episode is defined as the presence of 5 or more of the 9 core symptoms of major depression for at least 2 weeks. The symptoms include: depressed mood; loss of interest; weight loss (or other weight or appetite changes); insomnia or hypersomnia; agitation or psychomotor retardation; fatigue; feelings of worthlessness or guilt; impaired concentration; suicidal thinking or behaviour. One of the 5 symptoms must be either

depressed mood or loss of interest in activities. Another essential feature of major depression is the presence of significant distress or impairment in social, occupational, or other important areas of functioning. A seasonal major depressive episode is defined by the identical features.

Labelling includes a "black box" warning concerning the increased risk of suicidal thoughts and behaviour in paediatric patients treated with antidepressant medications.

Reference: *FDA News*, P06-79. 12 June 2006.

Decitabine approved for myelodysplastic syndromes

United States of America — The Food and Drug Administration (FDA) has approved decitabine (Dacogen) injection for the treatment of myelodysplastic syndromes (MDS). Dacogen is a new molecular entity that has received orphan drug status.

Decitabine is thought to work by promoting normal development of blood cells. Different types of MDS exist, resulting in different manifestations of the disease. MDS can develop following treatment with drugs or radiation therapy for other diseases or it can develop without any known cause. Some forms of MDS can progress to acute myeloid leukaemia (AML), a type of cancer in which too many white blood cells are made.

An estimated 7000 to 12 000 new cases of MDS are diagnosed yearly in the United States. Although MDS occurs in all age groups, the highest prevalence is in people over 60 years of age. Typical symptoms include weakness, fatigue, infections, easy bruising, bleeding, and fever.

The most common side effects reported in clinical trials included neutropenia (low white blood cell count), thrombocytopenia (low platelets in blood), anaemia, fatigue, fever, nausea, cough, bleeding in the skin, constipation, diarrhoea, and hyperglycaemia (high blood sugar).

Reference: *FDA News.* P06-72, 22 May 2006.

Medical device innovation initiative

United States of America — The Food and Drug Administration (FDA) is launching the Medical Device Innovation Initiative to make new medical devices available more quickly for patients. This broad initiative will promote early interaction between the FDA and industry to optimize review times and foster innovation.

With the convergence of many scientific and technology breakthroughs, the pace of medical invention is accelerating, inspiring hope for better health outcomes with less invasive procedures and shorter recovery times. As part of this initiative, new guidelines provide recommendations on the use of Bayesian statistical methods in the design and analysis of medical device clinical trials. The use of Bayesian statistics offers industry the option of using prior, legally available information about safety and/or effectiveness in a mathematically acceptable way to design more efficient clinical trials, while still maintaining scientific rigor.

Reference: *FDA News*, P06-64. 3 May 2006.

Topotecan/cisplatin for late–stage cervical cancer

United States of America — The Food and Drug Administration (FDA) has approved a combination of topotecan hydrochloride (Hycamtin®) and cisplatin for use as the first drug treatment for women with late-stage cancer of the cervix when a physician determines that surgery or radiation therapy are unlikely to be effective. The approval includes a new indication for topotecan, which was approved in 1996 for treating ovarian cancer and in 1998 for small cell lung cancer.

The combination of topotecan and cisplatin is specifically indicated for women with Stage IVB (incurable), recurrent, or persistent cancer of the cervix which spreads to other organs and is not likely to respond to treatment with surgery or radiation.

In clinical trials, the combination significantly improved survival compared to the use of cisplatin alone. Patients on combined therapy survived about three months longer than patients on cisplatin alone.

Topotecan is associated with a significant risk of neutropenia, a condition which makes it more difficult for the body to fight infections. Serious side effects also include thrombocytopenia, a decrease in blood platelets that can lead to excessive bleeding and anaemia. Less serious side effects include nausea and vomiting. The incidences of neutropenia, anaemia, and thrombocytopenia were significantly increased among patients receiving the combination treatment compared to those receiving cisplatin alone, as were nausea and vomiting, mucositis, rash, and liver toxicity.

Reference: *FDA News,* P06-81.15 June 2006.

Rapid approval of vaccine for prevention of cervical cancer

United States of America — The Food and Drug Administration (FDA) has announced the approval the first vaccine developed to prevent cervical cancer, precancerous genital lesions and genital warts due to human papillomavirus (HPV). The vaccine is approved for use in females 9–26 years of age. Gardasil® was evaluated and approved in six months under FDA's priority review process—a process for products with potential to provide significant health benefits.

HPV is the most common sexually-transmitted infection in the United States. Worldwide, cervical cancer is the second most common cancer in women, and is estimated to cause over 470 000 new cases and 233 000 deaths each year.

For most women, the body's own defence system will clear the virus and infected women do not develop related health problems. However, some HPV types can cause abnormal cells on the lining of the cervix that years later can turn into cancer. Other HPV types can cause genital warts. The vaccine is effective against HPV types 16 and 18, which cause approximately 70 percent of cervical cancers and against HPV types 6 and 11, which cause approximately 90 percent of genital warts.

Gardasil® is a recombinant vaccine that is given as three injections over a six-month period. Immunization is expected to prevent most cases of cervical cancer due to HPV types included in the vaccine. However, females are not protected if they have been infected prior to vaccination, indicating the importance of immunization before potential exposure to the virus. Also, Gardasil® does not protect against less common HPV types not included in the vaccine, thus routine and regular pap screening remain critically important to detect precancerous changes in the cervix to allow treatment before cervical cancer develops.

The safety of the vaccine was evaluated in approximately 11 000 individuals. Most adverse experiences included mild or moderate local reactions, such as pain or tenderness at the site of injection. The manufacturer has agreed to conduct several studies following licensing, including additional studies to further evaluate general safety and long-term effectiveness. The manufacturer will also monitor the pregnancy outcomes of women who receive Gardasil® while unknowingly pregnant. Also, the manufacturer has an ongoing study to evaluate the safety and effectiveness in males.

Reference: *FDA News,* P06-77. 8 June 2006. http://www.fda.gov/womens/getthefacts/hpv.html

Rasagiline approved for Parkinson disease

United States of America —The Food and Drug Administration has approved rasagiline (Azilect®), a new molecular entity, for the treatment of Parkinson disease. The drug is a monoamine oxidase type—B (MAO-B) inhibitor that blocks the breakdown of dopamine.

Rasagiline was approved for use as an initial single drug therapy in early Parkinson disease, and as an addition to levodopa in more advanced patients. Rasagiline may be associated with hypertensive crisis if patients also consume tyramine-rich foods and beverages (such as cheese and red wine) or dietary supplements or amines contained in many cough/cold medications. Therefore, patients will need to avoid these sources of tyramine and amines when taking rasagiline. As with many other medications for Parkinson, rasagiline has the potential to cause dyskine-

sias, hallucinations and lowered blood pressure. These side effects are described in the product labelling.

During development, melanoma was diagnosed in a small number of patients treated with rasagiline. Although the FDA has concluded that the available data do not establish that Azilect® is associated with an increased risk for melanoma, it appears that compared to the general population, patients with Parkinson disease have an increased risk for this form of skin cancer. The drug's manufacturer will perform a Phase IV postmarket study and the product labelling will recommend that patients undergo periodic dermatologic examinations.

Reference: *FDA News,* P06-68. 17 May 2006

Fluoxetine approved for children and adolescents

European Union — The European Medicines Agency (EMEA) has recommended to extend the indication for fluoxetine (Prozac®) and associated names to include the treatment of children of 8 years of age or older who suffer from moderate to severe depression and who do not respond to psychological therapy. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of using fluoxetine in this indication outweigh its potential risks, but that the marketing authorization holder (MAH), should carry out additional studies to ensure that the safety profile of fluoxetine remains acceptable.

Prozac® and associated names is authorized in most EU Member States for the treatment of major depressive episodes, obsessive-compulsive disorder and bulimia nervosa in adults.

Based on the data, the CHMP concluded:

- The studies in children and adolescents showed a positive effect.
- Prozac® should only be used together with psychological therapy in patients non-responding to such therapy alone after 4 to 6 sessions.
- The starting dose should be 10 mg per day (given as 2.5 ml of oral solution) and may be increased to 20 mg per day after one to two weeks.
- If no clinical benefit is seen within 9 weeks, treatment should be reconsidered.
- The significance of the observations in animal studies on sexual development, emotional behaviour and testicular toxicity will be further investigated. The MAH will also put in place a system to obtain safety data in treated children, in particular regarding sexual development.
- The CHMP confirmed that doctors and parents should carefully monitor children and adolescents for suicidal behaviour, particularly at the beginning of treatment.

Reference: European Medicines Agency. European Medicines Agency adopts a positive opinion for the use of Prozac® in the treatment of children and adolescents suffering from depression. *Press Release*. 6 June 2006. EMEA/202554/2006.

Withdrawal of marketing application for Surfaxin®

European Union — The European Medicines Agency has been formally notified by the manufacturer of the orphan medicinal product Surfaxin® of their decision to withdraw the application for a centralized marketing authorization. The active substances of Surfaxin® are sinapultide, dipalmitoyl-phosphatidylcholine, palmitoyloleoyl phosphatidylglycerol and palmitic acid for the prevention and treatment of respiratory distress syndrome in premature babies.

At the time of the withdrawal, the application was under review by the Committee for Medicinal Products for Human Use (CHMP). In its official withdrawal letter, the company stated that the withdrawal was due to manufacturing and clinical issues. More information about Surfaxin® and the current state of the scientific assessment at the time of withdrawal will be made available in a question and answer document to be published on the EMEA website at http://www.emea.eu.int.

Reference: *Press release*. European Medicines Agency. Doc. Ref. EMEA/211505/2006, 8 June 2006. http://www.emea.eu.int

Resumed marketing of natalizumab

United States of America — The Food and Drug Administration (FDA) has approved an application for resumed marketing of natalizumab (Tysabri®) subject to a special restricted distribution programme. Natalizumab is a monoclonal antibody used to treat patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of exacerbations (flare-ups). Natalizumab is indicated for use as monotherapy since its use with other immune modifying drugs could impact risk. It is also meant for patients who have not responded adequately to, or cannot tolerate, other treatments for MS.

Tysabri® was initially approved by the FDA in November 2004, but was withdrawn by the manufacturer in February 2005 after three patients in the drug's clinical trials developed progressive multifocal leukoencephalopathy (PML), a serious and rare viral infection of the brain. Two of the cases were fatal. Based on this information, FDA put clinical trials of the drug on hold in February 2005. FDA allowed a clinical trial to resume in February 2006, following a re-examination of the patients who had participated in the previous clinical trials, confirming that there were no additional cases of PML.

The Peripheral and Central Nervous Systems Drugs Advisory Committee recommended a risk-minimization programme with mandatory patient registration and periodic follow-up. Natalizumab will only be prescribed, distributed, and infused by prescribers, infusion centres, and pharmacies registered with the programme.

Reference: *FDA News*, P06-75. 6 June 2006

EU Regulation on compulsory licensing published

The European Union regulation text on compulsory licensing of patents relating to the manufacture of pharmaceutical products for export to countries with public health problems was published in the Official Journal of the EU on 9 June 2006. It entered into force on the twentieth day following that of its publication in the *EU Official Journal*, i.e, 29 June 2006.

Reference: http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_157/l_15720060609en00010007.pdf

Emerging Diseases

Tissue infectivity and transmissible spongiform encephalopathies

A variant form of a fatal brain disease, Creutzfeldt-Jakob disease (vCJD), was first identified in the mid-1990s as a result of suspected bovine spongiform encephalopathy (BSE) transmission to humans in the United Kingdom. Since then, cases of vCJD have occurred in Canada, France, Ireland, Italy, Japan, Netherlands, Portugal, Saudi Arabia, Spain, USA, and the United Kingdom,

Until recently, all vCJD cases were attributed to consumption of beef products contaminated with the infectious agent of BSE. However, since December 2003, three individuals have been identified with vCJD infections probably acquired from blood transfusions. The fact that the three vCJD infections followed transfusions from clinically healthy persons who became ill more than a year after donating blood implies that other blood donors who might currently be incubating the disease could also be potential sources of infection. The possible extent of future blood-borne spread of vCJD infections is still unknown. The identification of these cases has intensified the concern about possible unmapped ways in which the disease might spread. Except for the three transfusion-transmitted infections, no cases of vCJD have been linked to any medicinal product to date, and guidelines have been developed by the World Health Organization (WHO) and other authorities to minimize the risk (1).

A consultation held at WHO in September 2005 brought together experts and regulators from around the world to revise existing *WHO Guidelines on Transmissible Spongiform Encephalopathies (TSEs) in relation to Biological and Pharmaceutical Products* (2) which recommended ways to prevent potential transmission of vCJD through human blood and blood products, or medicinal products prepared with bovine derived materials. The primary objective of the Consultation was to provide evidence-based information to national regulatory authorities to assist in conducting risk assessments and selecting measures to reduce the risk of transmitting vCJD through human blood and blood products and other medicinal products of biological origin. These and other issues discussed during the consultation have now been published as *WHO Guidelines on tissue infectivity distribution in transmissible spongiform encephalopathies* and are available on the WHO website (3). The Guidelines ensure that all national regulatory authorities with limited resources have ready access to reliable and up-to-date information when assessing TSE risks and evaluating product safety.

WHO consultations have repeatedly encouraged authorities to consider introducing precautionary measures to minimize possible risks to blood and blood products while not compromising supply and have stressed that tissues or body fluids of ruminant origin should be avoided in the preparation of biological and pharmaceutical products. When bovine materials must be used, they should be obtained from sources assessed to have negligible risk from the infectious agent of BSE. Most bovine tissues and bovine muscle used to manufacture biologicals have little risk of contamination with BSE agent if carefully selected and collected according to guidelines.

Bovine blood has not been identified as a source of infection, and properly collected fetal bovine serum has a negligible risk. However, the blood of sheep with experimental BSE or natural scrapie can be infectious and, because scrapie and BSE agents behave similarly in sheep and goats, the blood of small ruminants should either be avoided in preparing biologicals or selected very carefully from sources known to be free of TSEs.

Current knowledge concerning major categories of infectivity is set out on the following pages.

Major categories of infectivity tables

The information set out in the following tables is based exclusively upon observations of naturally occurring disease, or primary experimental infection by the oral route in ruminants, and does not include data on models using strains of transmissible spongiform encephalopathy (TSE) adapted to experimental animals, because passaged strain phenotypes can differ significantly and unpredictably from those of naturally occurring disease. Also, because detection of misfolded host prion protein (Pr^{PTSE}) has proven to be a reliable indicator of infectivity, Pr^{PTSE} testing results have been presented in parallel with bioassay data. Tissues are grouped into three major infectivity categories, irrespective of the stage of disease:

A: High-infectivity tissues: central nervous system (CNS) tissues that attain a high titre of infectivity in the later stages of all TSEs, and certain tissues that are anatomically associated with the CNS.

B: Lower-infectivity tissues: peripheral tissues that have tested positive for infectivity and/or Pr^{PTSE} in at least one form of TSE.

C: Tissues with no detectable infectivity: tissues that have been examined for infectivity and/or Pr^{PTSE} with negative results.

Data entries are shown as follows:

+	Presence of infectivity or Pr^{PTSE}
-	Absence of detectable infectivity or Pr^{PTSE}
NT	Not tested
NA	Not applicable
?	Controversial results
( )	Limited or preliminary data

The placement of a given tissue in one or another category can be disease-specific and subject to revision as new data accumulate from increasingly sensitive tests. In fact, it is conceivable that the detection of infectivity using transgenic mice that over-express genes encoding various prion proteins, or the detection of Pr^{PTSE} using some newly developed amplification methods, might prove to be more sensitive than transmission studies in wild-type bioassay animals, and thus may not correlate with disease transmission in nature.

It is also important to understand that categories of infectivity are not the same as categories of risk, which require consideration not only of the level of infectivity in tissue, but also of the amount of tissue to which a person or animal is exposed, and the route by which infection is transmitted. For example, although the level of tissue infectivity (concentration of infectivity in tissue as reflected by titre) is the most important factor in estimating the risk of transmission by instrument cross contamination during surgical procedures (e.g., neurosurgery versus general surgery), it is only one determinant of the risk of transmission by blood transfusions, in which a large amount of lowinfectivity material is administered directly into the circulation, or the risk of transmission by food that, irrespective of high or low infectivity, involves the comparatively inefficient oral route of infection.

Table A: High-infectivity tissues

CNS tissues that attain a high titre of infectivity in the later stages of TSE and certain tissues anatomically associated with the CNS								
Tissues	**Human TSEs**				**Cattle**		**Sheep & goats**	
	vCJD		**Other TSEs**		**BSE**		**Scrapie**	
	Infect-ivity[1]	PrP^{TSE}	Infect-1 ivity[1]	PrP^{TSE}	Infect-ivity[1]	PrP^{TSE}	Infect-ivity[1]	PrP^{TSE}
Brain	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+
Retina	NT	+	+	+	+	NT	NT	+
Optic nerve[2]	NT	+	NT	+	+	NT	NT	+
Spinal ganglia	+	+	NT	+	+	NT	NT	+
Trigeminal ganglia	+	+	NT	+	+	NT	NT	+
Pituitary gland[3]	NT	+	+	+	-	NT	+	NT
Dura mater[3]	NT	-	+	-	NT	NT	NT	NT

Footnotes:

1. Infectivity bioassays of human tissues have been conducted in either primates or mice (or both); bioassays of cattle tissues have been conducted in either cattle or mice (or both); and most bioassays of sheep and/or goat tissues have been conducted only in mice. In regard to sheep and goats, not all results are consistent for both species.

2. In experimental models of TSE, the optic nerve has been shown to be a route of neuroinvasion and contains high titres of infectivity.

3. No experimental data about infectivity in human pituitary gland or dura mater have been reported, but cadaveric dura mater allograft patches, and growth hormone derived from cadaveric pituitaries have transmitted disease to hundreds of people and therefore must be included in the category of high-risk tissues.

Table B: Lower-infectivity tissues

Peripheral tissues that have tested positive for infectivity and/or PrPTSE in at least one form of TSE								
Tissues	**Human TSEs**				**Cattle**		**Sheep & goats**	
	vCJD		**Other TSEs**		**BSE**		**Scrapie**	
	Infect-ivity[1]	PrP^{TSE}	Infect-ivity[1]	PrP^{TSE}	Infect-ivity[1]	PrP^{TSE}	Infect-ivity[1]	PrP^{TSE}
Peripheral nervous system								
Peripheral nerves	+	+	(-)	+	+	+	+	+
Enteric plexuses[4]	NT	+	NT	(-)	NT	+	NT	+

.../...

Table B: Lower-infectivity tissues (continued)

Peripheral tissues that have tested positive for infectivity and/or PrP^{TSE} in at least one form of TSE								
Tissues	**Human TSEs**				**Cattle**		**Sheep & goats**	
	vCJD		**Other TSEs**		**BSE**		**Scrapie**	
	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}
Lymphoreticular tissues								
Spleen	+	+	+	+	-	-	+	+
Lymph nodes	+	+	+	-	-	-	+	+
Tonsil	+	+	NT	-	+	-	+	+
Nictitating membrane	NA	NA	NA	NA	+	-	NT	+
Thymus	NT	+	NT	-	-	NT	+	NT
Alimentary tract								
Esophagus	NT	-	NT	-	-	NT	NT	+
Fore-stomach[5] (ruminants only)	NA	NA	NA	NA	-	NT	NT	+
Stomach/ abomasum[6]	NT	-	NT	NT	-	NT	NT	+
Duodenum	NT	-	NT	NT	-	NT	NT	+
Jejunum[6]	NT	+	NT	-	-	NT	NT	+
Ileum[6, 7]	NT	+	NT	-	+	+	+	+
Appendix	-	+	NT	-	NA	NA	NA	NA
Large intestine[6]	+	+	NT	-	-	NT	+	+
Reprductive tissues								
Placenta[8]	NT	-	(+)	-	-	NT	+	+
Other tissues								
Lung	NT	-	+	-	-	NT	-	-
Liver	NT	-	+	-	-	NT	+	NT
Kidney	NT	-	+	-	-	-	-	-
Adrenal	NT	+	-	-	NT	NT	+	NT
Pancreas	NT	-	NT	-	-	NT	+	NT
Bone marrow	-	-	(-)	-	(+)	NT	+	NT
Skeletal muscle[9]	NT	+	(-)	+	(+)	NT	-	+
Tongue[10]	NT	-	NT	-	-	NT	NT	+
Blood vessels	NT	+	NT	+	-	NT	NT	+
Nasal mucosa[11]	NT	NT	NT	+	-	NT	+	+
Salivary gland	NT	-	NT	NT	-	NT	+	NT
Cornea[12]	NT	-	+	-	NT	NT	NT	NT
Body fluids								
CSF	-	-	+	-	-	NT	+	NT
Blood[13]	+	?	-	?	-	?	+	?

Footnotes:

4. In cattle, PrP^{TSE} was limited to enteric plexus in the distal ileum.

5. Ruminant fore-stomachs (reticulum, rumen, and omasum) are widely consumed, as is the true stomach (abomasum). The abomasum of cattle (and sometimes sheep) is also a source of rennet.

6. In vCJD, transmission to mice has so far been limited to rectal tissue, and PrP^{TSE} was detected only in gut-associated lymphoid and nervous tissue (mucosa, muscle, and serosa were negative). In goats, PrPTSE was also limited to gut-associated lymphoid and nervous tissue [Andreoletti, unpublished data]

7. In cattle and sheep, only the distal ileum has been bioassayed for infectivity.
8. A single report of transmission of CJD infectivity from human placenta has never been confirmed and is considered improbable.
9. Muscle homogenates have not transmitted disease to primates from humans with sCJD, or to cattle from cattle with BSE. However, intracerebral inoculation of a semitendinosus muscle homogenate (including nervous and lymphatic elements) from a single cow with BSE has transmitted disease to PrP over-expressing transgenic mice at a rate indicative of only trace levels of infectivity. Also, recent published and unpublished studies have reported the presence of PrP^{TSE} in skeletal muscle in experimental rodent models of scrapie and vCJD, in experimental and natural infections of sheep and goats, in sheep orally dosed with BSE [Andreoletti, unpublished data], and in humans with sCJD, iCJD and vCJD. Bioassays to determine whether PrP^{TSE} is associated with transmissibility in these experimental or natural infections are in progress.
10. In cattle, infectivity bioassay was negative, but the presence of PrP^{TSE} in palatine tonsil has raised concern about possible infectivity in lingual tonsillar tissue at the base of the tongue that may not be removed at slaughter.
11. In sCJD, PrP^{TSE} is limited to olfactory mucosa.
12. Because only one or two cases of CJD have been plausibly attributed to corneal transplants among hundreds of thousands of recipients, cornea is categorised as a lower-risk tissue; other anterior chamber tissues (lens, aqueous humor, iris, conjunctiva) have been tested with a negative result both in vCJD and other human TSEs, and there is no epidemiological evidence that they have been associated with iatrogenic disease transmission.
13. A wealth of data from studies of blood infectivity in experimental animal models of TSE has been extended by recent studies documenting infectivity in the blood of sheep with naturally occurring scrapie, and (from epidemiological observations) three blood-associated vCJD transmissions in humans. Blood has not been shown to transmit disease from patients with any other form of TSE, or from cattle with BSE (including fetal calf blood). However, several laboratories using new, highly sensitive methods to detect PrP^{TSE} claim success in studies of plasma and/or buffy coat in a variety of animal and human TSEs. Because the tests are all in a preliminary stage of development (and do not yet include results on blinded testing of specimens from naturally infected humans or animals), the Consultation felt that it was still too early to evaluate the validity of these tests with sufficient confidence to permit either a negative or positive conclusion.

Table C: Tissues with no detected infectivity or PrP^{TSE}

Tissues	Human TSEs				Cattle		Sheep & goats	
	vCJD		Other TSEs		BSE		Scrapie	
	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}
Reproductive issues								
Testis	NT	-	(-)	-	-	NT	-	NT
Prostate/ Epididymis/ Seminal vesicle	NT	-	(-)	-	-	NT	-	NT
Semen	NT	-	(-)	-	-	NT	NT	NT
Ovary	NT	-	NT	-	-	NT	-	NT
Uterus (non-gravid)	NT	-	NT	-	-	NT	-	NT
Placenta fluids	NT	NT	(-)	NT	-	NT	NT	NT
Fetus[14]	NT	NT	NT	NT	-	NT	-	-
Embryos[14]	NT	NT	NT	NT	-	NT	?	NT
Musculoskeletal tissues								
Bone	NT	NT	NT	NT	-	NT	NT	NT
Heart/ pericardium	NT	-	-	-	-	NT	-	NT
Tendon	NT	NT	NT	NT	-	NT	NT	NT

Table C: Tissues with no detected infectivity or PrP^{TSE} (continued)

Tissues	Human TSEs				Cattle		Sheep & goats	
	vCJD		Other TSEs		BSE		Scrapie	
	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}	Infectivity[1]	PrP^{TSE}
Other tissues								
Gingival tissue	NT	-	-	-	NT	NT	NT	NT
Dental pulp	NT	-	NT	-	NT	NT	NT	NT
Trachea	NT	-	NT	-	-	NT	NT	NT
Skin	NT	-	NT	-	-	NT	-	NT
Adipose tissue	NT	-	(-)	-	-	NT	NT	NT
Thyroid gland	NT	-	(-)	-	NT	NT	-	NT
Mammary gland/ udder	NT	NT	NT	NT	-	NT	-	NT
Body fluids, secretions and excretions								
Milk[15]	NT	NT	(-)	NT	-	-	-	NT
Colostrum[16]	NT	NT	(-)	NT	(-)	-	-	NT
Cord blood[17]	NT	NT	(-)	NT	-	NT	NT	NT
Saliva	NT	-	-	NT	NT	NT	-	NT
Sweat	NT	NT	-	NT	NT	NT	NT	NT
Tears	NT	NT	-	NT	NT	NT	NT	NT
Nasal mucus	NT	-	-	NT	NT	NT	NT	NT
Bile	NT	NT	NT	NT	NT	NT	NT	NT
Urine[16, 17]	NT	NT	-	-	-	NT	NT	NT
Feces	NT	NT	-	NT	-	NT	-	NT

14. Embryos from BSE-affected cattle have not transmitted disease to mice, but no infectivity measurements have been made with fetal calf tissues other than blood (negative mouse bioassay). Calves born of dams that received embryos from BSE-affected cattle have survived for observations periods of up to seven years, and examination of the brains of both the unaffected dams and their offspring revealed no spongiform encephalopathy or PrPTSE .

15. Evidence that infectivity is not present in milk includes temporo-spatial epidemiologic observations failing to detect maternal transmission; clinical observations of over a hundred calves nursed by infected cows that have not developed BSE; and experimental observations that milk from infected cows has not transmitted disease when administered intracerebrally or orally to mice. Also, PrPTSE has not been detected in milk from cattle incubating BSE following experimental oral challenge.

16. Early reports of transmission of CJD infectivity from human cord blood, colostrum, and urine have never been confirmed and are considered improbable. A recent bioassay in PrP over-expressing transgenic mice of colostrum from a cow with BSE gave a negative result; and PrPTSE has not been detected in colostrum from cattle incubating BSE following experimental oral challenge.

17. IgG short chains mimicking the Western blot behavior of PrPTSE have been identified in the urine of sporadic, variant, and familial CJD patients.

ATC/DDD Classification

ATC/DDD Classification (temporary)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology 22–23 March 2006. Comments or objections to the decisions should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology at whocc@fhi.no before 1 September 2006. If no objections are received before this date, the new ATC codes and DDDs will be considered final and be included in the January 2007 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted through e-mail at: whocc@fhi.no.

ATC level	INN/Common name	ATC code
New ATC level codes (other than 5th level):		
	Agents for age related macular degeneration	S01L[1]
	Angiotensin II antagonists and calcium channel blockers	C09DB
	Antivirals for treatment of HIV infections, combinations	J05AR[2]
	Insulins and analogues, for inhalation	A10AF
	Ocular antineovascularization agents	S01LA
	Papillomavirus vaccines	J07BM

[1] *For the complete classification of S01L, see Summary of the main ATC alterations*
[2] *For the complete classification of J05AR, see Summary of the main ATC alterations*

New ATC 5th level codes:		
	abatacept	L04AA24
	aliskiren	C09XA02
	ambrisentan	C02KX02
	dasatinib	L01XE06
	deferasirox	V03AC03
	desvenlafaxine	N06AX23
	emtricitabine, tenofovir disoproxil and efavirenz	J05AR06
	fluocinolone acetonide	S01BA15
	gadofosveset	V08CA11
	garenoxacin	J01MA19
	insulin (human)	A10AF01
	medical air	V03AN05
	nelarabine	L01BB07
	nitrous oxide, combinations	N01AX63
	panitumumab	L01XC08

ATC level	INN/Common name	ATC code
	papillomavirus (human types 6, 11, 16, 18)	J07BM01
	papillomavirus (human types 16, 18)	J07BM02
	ranibizumab	S01LA04
	sapropterin	A16AX07
	sitagliptin	A10BX05
	telbivudine	J05AF11
	valsartan and amlodipine	C09DB01
	varenicline	N07BA03
	vildagliptin	A10BX06
	zidovudine, lamivudine and nevirapine	J05AR05
	zoster, live attenuated	J07BK02

ATC code changes *(changes will not be implemented before January 2007)*

INN/common name	Previous ATC	New ATC
anecortave	S01XA16	S01LA02
glyceryl trinitrate	D03AX07	C05AX06
isosorbide dinitrate	D03AX08	C05AX07
lamivudine and abacavir	J05AF30[1]	J05AR02
pegaptanib	S01XA17	S01LA03
tenofovir disoproxil and emtricitabine	J05AF30[1]	J05AR03
verteporfin	L01XD02	S01LA01
zidovudine and lamivudine	J05AF30[1]	J05AR01
zidovudine, lamivudine and abacavir	J05AF30[1]	J05AR04

[1] *J05AF30: ATC level name: Combinations*

ATC name changes

Previous	New	ATC code
Cytokines and immunomodulators	Cytokines and immuno-modulators/stimulants	L03A
Immunostimulants	Immunomodulators/stimulants	L03
Immunosuppressive agents	Immunomodulators/suppressants	L04
Insulins and analogues, fast-acting	Insulins and analogues, fast-acting, for injection	A10AB
Insulins and analogues, intermediate-acting	Insulins and analogues intermediate-acting, for injection	A10AC
Insulins and analogues, intermediate-acting combined with fast-acting	Insulins and analogues, intermediate-acting combined with fast-acting, for injection	A10AD
Insulins and analogues, long-acting	Insulins and analogues, long-acting, for injection	A10AE
Other cytokines and immunomodulators modulators/stimulants	Other cytokines and immuno-	L03AX
Other immunosuppressive agents	Other immunomodulators/ suppressants	L04AX
Selective immunosuppressive agents	Selective immunomodulators/ suppressants	L04AA

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
entecavir	0.5	mg	O	J05AF10
erdosteine	0.6	g	O	R05CB15
estradiol	7.5	mcg	V[1]	G03CA03
hydroxybutyric acid	7.5	g	O	N07XX04
ibuprofen	30	mg[2]	P	C01EB16
ivabradine	10	mg	O	C01EB17
natalizumab	10	mg	P	L04AA23
posaconazole	0.8	g	O	J02AC04
tipranavir	1	g	O	J05AE09

[1] vaginal ring, refers to amount delivered per 24 hours
[2] course dose

Change of DDDs *(Note that changes will not be implemented before January 2007)*

INN/common name	Previous DDD	New DDD	ATC Code
cefditoren	0.6 g O*	0.4 g O	cefditoren

** Temporary DDD from October 2005, has not been included in the ATC index.*

ATC/DDD Classification

ATC/DDD classification (final)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology in October 2005 They came into force on 1 February 2006 and will be included in the January 2007 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted through e-mail at: whocc@fhi.no.

ATC level	INN/Common name	ATC code
New ATC level codes (other than 5th level):		
	Protein kinase inhibitors	L01XE
New ATC 5th level codes:		
	aceclofenac	M02AA25
	alendronic acid and colecalciferol	M05BB03
	carteolol, combinations	S01ED55
	ciprofloxacin	S02AA15
	clindamycin, combinations	D10AF51
	daptomycin	J01XX09
	darunavir	J05AE10
	diclofenac	D11AX18
	diphtheria-*Haemophilus influenzae* B-pertussis-tetanus-hepatitis B	J07CA11
	diphtheria-pertussis-poliomyelitis-tetanus-hepatitis B	J07CA12
	exenatide	A10BX04
	febuxostat	M04AA03
	glimepiride and rosiglitazone	A10BD04
	glucarpidase	V03AF09
	idursulfase	A16AB09
	lenalidomide	L04AX04
	moxifloxacin	S01AX22
	paliperidone	N05AX13
	palonosetron	A04AA05
	parathyroid hormone	H05AA03
	pazufloxacin	J01MA18
	pitavastatin	C10AA08
	sorafenib	L01XE05
	stiripentol	N03AX17
	sunitinib	L01XE04
	tigecycline	J01AA12

ATC code changes *(changes will not be implemented before January 2007)*

INN/common name	Previous ATC	New ATC
erlotinib	L01XX34	L01XE03
gefitinib	L01XX31	L01XE02
imatinib	L01XX28	L01XE01
ribavirin, combinations*	J05AB54	L03AB60

** See list of changed ATC level names*

ATC name changes

Previous	New	ATC code
Bisphosphonates and calcium, sequential preparations	Bisphosphonates, combinations	M05BB
Etidronic acid and calcium	Etidronic acid and calcium, sequential	M05BB01
Oral Blood glucose lowering drugs	Blood glucose lowering drugs, excluding insulins	A10B
Other oral blood glucose lowering drugs	Other blood glucose lowering drugs, excluding insulins	A10BX
Ribavirin, combinations	Peginterferon alfa-2b, combinations	L03AB60**
Risedronic acid and calcium	Risedronic acid and calcium, sequential	M05BB02
Varicella vaccines	Varicella zoster vaccines	J07BK
Varicella, live attenuated	Varicella zoster, live attenuated	J07BK01

*** See list of changed ATC codes*

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
benfluorex	0.45	g	O	C10AX04
cefditoren	0.6	g	O	J01DD16
cyanocobalamin	70	mcg	N	B03BA01
daptomycin	0.28	g	P	J01XX09
desmopressin	0.36	g base	SL	H01BA02
ibandronic acid	5	mg	O	M05BA06
imidapril	10	mg	O	C09AA16
interferon alfa natural	2	MU	P	L03AB01
lanreotide	3	mg	P	H01CB03
mecobalamin	1.5	mg	O	B03BA05
mecobalamin	0.2	mg	P	B03BA05
mesna	1.2	g	Inhal	R05CB05
naftidrofuryl	0.6	g	O	C04AX21
palifermin	4.2	mg	P	V03AF08
palonosetron	0.25	mg	P	A04AA05
pazufloxacin	1	g	P	J01MA18
piribedil	0.2	g	O	N04BC08
pitavastatin	2	mg	O	C10AA08
pyritinol	0.6	g	O	N06BX02
rasagiline	1	mg	O	N04BD02
tegaserod	12	mg	O	A03AE02

New DDDs (continued):

INN/common name	DDD	Unit	Adm.R	ATC code
testosterone	60	mg	SL	G03BA03
tianeptine	37.5	mg	O	N06AX14
trimebutine	0.6	g	O	A03AA05
ziconotide	12	mcg	P	N02BG08

Change of DDDs *(changes to be implemented in January 2007)*

INN/common name	Previous DDD		New DDD		ATC Code
cinacalcet	90 mg	O*	60 mg	O	H05BX01
ibandronic acid	2.5 mg	O*	5 mg	O	M05BA06
ibandronic acid	4 mg	P	6 mg	P	M05BA06

** Temporary DDD, has not been included in the ATC index*

** Temporary DDD from October 2005, has not been included in the ATC index.*

Recent Publications, Information and Events

Interagency Emergency Health Kit 2006

Over the years, the concept of the emergency health kit has been adopted by many organizations and national authorities as a reliable, standardized and quickly available source of essential medicines and medical devices (renewables and equipment) urgently needed in a disaster situation.

The Interagency Emergency Health Kit 2006 (IEHK 2006) is now available on the WHO Medicines website. This is the third edition of the WHO Emergency Health Kit initially launched in 1990. This is an initiative of WHO in collaboration with a large number of organizations and agencies of the United Nations system and international and non-governmental organizations.

The aim of the emergency health kit is to encourage standardization of medicines and medical supplies (renewables and equipment) needed in emergencies and disasters. This will permit an effective response with medicines and medical devices by means of standard, pre-packed kits that could be kept in readiness to meet priority health needs in disaster situations. Its content is based on the health needs of 10 000 persons for a period of three months.

WHO encourages all countries, national and international organizations, agencies and donors to use The Interagency Emergency Health Kit 2006 when being called upon to respond urgently to emergencies or disasters.

Reference: http://www.who.int/medicines/publications/mrhealthkit.pdf

Therapeutic guidelines for rheumatology

The Therapeutic Guidelines range has become well known internationally. The guidelines are independent, peer reviewed and regularly updated. Therapeutic *Guidelines: Rheumatology,* have just been released covering management of a wide range of musculoskeletal conditions.

This title addresses several issues of current global interest. The section 'Getting to know Your Drugs' explains the role of appropriate drugs for the management of painful musculoskeletal conditions in an era where it has been hard to find safe new drugs for pain management.

This edition also features non-drug interventions and very clear diagrams and instructions for exercises which have been found to be most beneficial in the management of pain. Therapeutic Guidelines: Rheumatology also includes sections on children and adolescents and management of conditions during pregnancy and breastfeeding.

Reference: http://www.tg.com.au

Specifications for pharmaceutical preparations

The WHO Expert Committee on Specifications for Pharmaceutical Preparations meets every two years. The following is a list of reports and guidelines included in the Fortieth report of the Expert Committee recently published by WHO.

Annex 1 List of available International Chemical Reference Substances and International Infrared Reference Spectra.

Annex 2 Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms.

Annex 3 Supplementary guidelines on good manufacturing practices for the manufacture of herbal medicines.

Annex 4 Supplementary guidelines on good manufacturing practices: validation.

Annex 5 Good distribution practices for pharmaceutical products.

Annex 6 A model quality assurance system for procurement agencies.

Annex 7 Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability.

Annex 8 Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms.

Annex 9 Additional guidance for organizations performing in vivo bioequivalence studies.

Reference: WHO Expert Committee on Specifications for pharmaceutical preparations, Fortieth report. WHO Technical Report Series, No. 937, 2006 Available from: WHO Press, 1211 Geneva 27, Switzerland. Email: bookorders@who.int. Website and ordering on-line: http://www.who.int/bookorders.

New guidance for pharmacists on counterfeit medicines

The Medicines and Healthcare Products Regulatory Agency (MHRA) and the Royal Pharmaceutical Society of Great Britain (RPSGB) have published new guidance for pharmacists which explains the causes and consequences of counterfeiting and provides pharmacists with practical advice on detecting and reporting suspected counterfeit medicines.

Reference: Counterfeit medicines: Guidance for pharmacists. http://www.mhra.gov.uk/home/

Marketed unapproved drugs — policy guide

For historical reasons, some drugs are available in the United States that lack required FDA approval for marketing. The new drug approval and OTC drug monograph processes play an essential role in ensuring that all drugs are both safe and effective for their intended uses. Manufacturers of drugs that lack required approval, including those that are not marketed in accordance with an OTC drug monograph, have not provided evidence demonstrating safety and efficacy.

FDA is taking steps to either encourage the manufacturers of these products to obtain the required evidence and comply with approval provisions or remove the products from the market. In order to achieve these goals without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market, the FDA has issued *Guidance for FDA Staff and Industry. Marketed Unapproved Drugs — Compliance Policy Guide* which describes how FDA intend to exercise enforcement discretion with regard to drugs marketed in the United States that do not have required FDA approval for marketing. It applies to any drug required to have FDA approval for marketing, including new drugs covered by the Over-the-Counter (OTC) Drug Review, except for licensed biologics and veterinary drugs.

A brief, informal summary description of the various categories of these drugs and their regulatory status is provided in Appendix A as general background for the document. The manufacturers of these drugs have not received FDA approval to legally market

Reference: Food and Drug Administration. Center for Drug Evaluation and Research. http://www.fda.gov/cder/guidance/index.htm

WHO guidelines on avian influenza

WHO guidelines on avian influenza have been developed based on a rapid review of available evidence. These are available on the WHO Website.

Feedback on their usefulness would be very much appreciated, as they have been developed based on a rapid review of available evidence. The objective is to link recommendations explicitly to the quality of evidence currently available.

Reference: WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus. http://www.who.int/entity/csr/disease/

WHO analgesic ladder

An appraisal of the WHO Analgesic Ladder is the focus of the current issue of *Cancer Pain Release*, the publication of the WHO Pain and Palliative Care Communications Programme. The issue features an interview with Dr. Kathleen Foley, former chair of the WHO Expert Committee on Cancer Pain Relief and Active Supportive Care, the group that drafted Cancer pain relief (2). The WHO guidelines also include foundation measures for implementing cancer pain relief programmes and improving opioid availability.

The issue (available in English, French, Spanish and Russian) highlights research on the WHO Analgesic Ladder and provides online links to WHO source documents about the method to relieve cancer pain.

References

1. Cancer Pain Release, Volume 19, No 1, 2006 at http://www.WHOcancerpain.wisc.edu/feedback.html

2. World Health Organization. Cancer pain relief. With a guide to opioid availability (2nd ed.). 1996

Resources for paediatric formulations

The British Neonatal and Paediatric Pharmacists Group has many useful links on their Website. Under the “Pharmaceutical links” category there is a “Formulation and stability database”. The information in the database was gathered from hospitals throughout the UK and published documents.

Reference: http://www.nppg.org.uk/

Consultation Document

International Pharmacopoeia: Revision of monographs for antimalarials and draft proposals for antiretrovirals

All monographs published in *The International Pharmacopoeia* on artemisin derivatives, (i.e. artemether, artemisinin, artemotil, and artenimol as active ingredients and dosage forms) have the same limits for the related substances tests (HPLC and TLC) with the exception of artesunate. Artesunate (active ingredient and tablets) has higher limits than the others due to the fact that this substance was considered to be less stable. However, comments received from different parties and experimental verification by the WHO Collaborating Centre for Drug Quality Assurance, People's Republic of China, suggest that the limits on artesunate should be reconsidered and brought in line with the other *International Pharmacopoeia* monographs on artemisinin derivatives. In addition, in all monographs on artemisinin derivatives except artesunate, a test for loss of drying is described. For artesunate, a test for water content is described. The proposals below would bring the monographs on artesunate in line with the other artemisinin derivative monographs.

Please address any comments you may have to: Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: kopps@who.int and rabouhansm@ who.int.

Artesunate

Related substances

It is proposed to amend the limits as follows:

HPLC

- Any impurity: not more than 0.5% (instead of 1.0%)
- Not more than one impurity above 0.25% (instead of 0.5%)
- Total of impurities: not more than 1.0% (instead of 2.0%)
- Disregard limit: 0.05% (instead of 0.1%)

TLC

- Any impurity spot is not more intense than 0.5% (instead of 1.0%)
- Not more than one impurity spot is more intense than 0.25% (instead of 0.5%)

HPLC assay limits

If it is agreed to revise the related substances tests as proposed above, consideration should be given to revising the HPLC assay limits to 97.0 %–102.0 % (instead of 96.0 %–102.0 %).

Water
It is proposed to replace the test for water by a test on loss of drying.

Drying at 60 ˚C under reduced pressure (not more than 2.67 kPa) has been suggested. The test could either specify drying to constant mass (as artemisinin) or specify a time, if a suitable time is available.

A suitable limit will need to be agreed (e.g. 0.5 % as for artemether or 1.0 % as for artenimol may be suitable).

Note: The basis in which the assay limits are calculated would need to be changed from the anhydrous to the dried substance.

Artesunate tablets

Related substances (HPLC and TLC)
If it is agreed to revise the limits in the related substances tests for the active ingredient, it is proposed that the limits for the tablets would need to be revised to maintain consistency.

International Pharmacopoeia: Draft proposals for antiretroviral dosage forms

Lamivudine oral solution

Draft proposal for The International Pharmacopoeia (May 2006). Please address any comments you may have to: Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: kopps@who.int and rabouhansm@ who.int.

Category. Antiretroviral (nucleoside reverse transcriptase inhibitor).

Storage. Lamivudine oral solution should be kept in a well-closed container, protected from light and at a temperature below 25 ˚C.

Additional Information: Strength in the current WHO Model List of Essential Medicines: 50 mg per 5 ml (10 mg per ml).

Requirements

Complies with the monograph for “Liquids for Oral Use”*.

[Note from Secretariat: A general monograph is in preparation.]

Definition. Lamivudine oral solution is a solution of Lamivudine in a suitable flavoured vehicle. It contains not less than 90.0 % and not more than 110.0 % of the amount of lamivudine, $C_8H_{11}N_3O_3S$ stated on the label.

** Refers to The International Pharmacopoeia*

Identity tests

A. Carry out test A.1. or where UV detection is not available, test A.2.

A.1. Carry out the test as described under 1.14.1 Thin-layer chromatography*, using silica gel R6 as the coating substance and a mixture of 67 volumes of dichloromethane R, 20 volumes of acetonitrile R, 10 volumes of methanol R and 3 volumes of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 10 µl of each of the following 2 solutions. For solution (A), dilute a volume of the oral solution containing 50 mg of Lamivudine to 50 ml with methanol R, filter, and use the filtrate. For solution (B), use 1.0 mg of lamivudine RS per ml of methanol. After removing the plate from the chromatographic chamber, allow it to dry in a current of cool air, and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity to that obtained with solution B.

A.2. Carry out the test as described under 1.14.1 Thin-layer chromatography*, using silica gel R5 as the coating substance and a mixture of 67 volumes of dichloromethane R, 20 volumes of acetonitrile R, 10 volumes of methanol R and 3 volumes of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 10 µl of each of the following 2 solutions. For solution (A), dilute a volume of the oral solution containing 50 mg of Lamivudine to 50 ml with methanol R, filter, and use the filtrate. For solution (B), use 1.0 mg of lamivudine RS per ml of methanol. After removing the plate from the chromatographic chamber, allow it to dry in a current of cool air. Spray with vanillin/sulfuric acid TS1. Heat the plate for a few minutes at 120 °C. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance, and intensity to that obtained with solution B.

B. See the test described below under Assay A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that obtained with solution (2).

C. The absorption spectrum of the final solution prepared for assay method B, when observed between 210 nm and 300 nm, exhibits one maximum at about 280 nm; the specific absorbance ($A^{1\%}$1cm) is between 577 to 637.

Related substances

Carry out the test as described under 1.14.4 high-performance liquid chromatography*, using a stainless steel column (25 cm x 4.6 mm) packed with base deactivated particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm) (Hypersil® BDS C18 is suitable). As the mobile phase, use a mixture of 5 volumes of methanol R and 95 volumes of buffer 3.8 (a 1.9 g/l solution of ammonium acetate R previously adjusted to pH 3.8 with glacial acetic acid R).

Prepare the following solutions. For solution (1), mix a quantity of the oral solution containing 50 mg of Lamivudine with sufficient mobile phase to produce 100 ml and filter. For solution (2), dilute 1.0 ml of solution (1) to 100 ml with mobile phase.

For the system suitability test: prepare solution (3) in the mobile phase containing about 10 µg of impurity B RS and 200 µg of lamivudine RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of about 277 nm. Maintain the temperature of the column at 35 °C.

** Refers to The International Pharmacopoeia*

Inject separately 20 µl each of solutions (1), (2) and (3). Record the chromatograms for about 3 times the retention time of lamivudine in solution (2). The test is not valid unless in the chromatogram obtained with solution (3) the resolution factor between the peaks due to lamivudine and impurity B is greater than 1.5.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). In the chromatogram obtained with solution (1), the area of any peak, other than the principal peak, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5 %), the area of not more than one such peak is greater than 0.7 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%), and the area of not more than two such peaks is greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3 %). The sum of the areas of all peaks, other than the principal peak, is not greater than 3 times the area of the principal peak obtained with solution (2) (3.0%). Disregard any peak with an area less than 0.05 times the area of the principal peak obtained with solution (2) (0.05 %).

Assay
Either test A or B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography*, using the conditions given above under Related Substances*. Prepare the following solutions in the mobile phase. For solution (1), mix a quantity of the oral solution containing 50 mg of Lamivudine with sufficient mobile phase to produce 100 ml and dilute 10 ml to 25 ml with mobile phase. Filter a portion of this solution through a 0.45 ìm filter, discarding the first few ml of the filtrate. For solution (2), use 0.2 mg of lamivudine RS per ml.

Inject 20 µl of solution (2) in six replicate injections into the chromatographic system. The assay is not valid unless the relative standard deviation for the peak area of lamivudine is less than 2.0 %

Inject separately 20 µl each of solutions (1) and (2).

Measure the areas of the peaks responses obtained in the chromatograms of solutions (1) and (2). Calculate the percentage content of lamivudine ($C_8H_{11}N_3O_3S$).

B. Dilute a volume of the oral solution containing 20 mg of Lamivudine to 50 ml with water. Add 1 ml of sulfuric acid (0.1 mol/l) VS and extract with two 30 ml quantities of diethyl ether R. Wash the combined ether extracts with 20 ml of water, combine the aqueous solutions and remove the ether using a current of nitrogen . Add sufficient water to produce 200 ml and dilute 5 ml to 50 ml with sulfuric acid (0.1 mol/l) VS. Measure the absorbance of the resulting solution in a 1 cm layer at the maximum at 280 nm against a solvent cell containing the blank. For the blank, use a solution prepared by diluting 1 ml of sulfuric acid (0.1 mol/l) VS to 200 ml with water and further dilute 5 ml of this solution to 50 ml with sulfuric acid (0.1 mol/l) VS. Calculate the percentage content of lamivudine, $C_8H_{11}N_3O_3S$ using the absorptivity value of 60.7 ($A^{1\%}$1cm = 607).

Lamivudine compressi
Lamivudine tablets

Draft proposal for The International Pharmacopoeia (May 2006). Please address any comments you may have to: Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: kopps@who.int and rabouhansm@ who.int.

Category. Antiretroviral (nucleoside reverse transcriptase inhibitor).

** Refers to The International Pharmacopoeia*

Storage. Lamivudine tablets should be kept in a well-closed container, protected from light.

Additional information. Strength in the current WHO Model List of Essential Medicines: 150 mg, 300 mg. The tablets may be uncoated or coated.

REQUIREMENTS

Comply with the monograph for "Tablets"*.

Lamivudine tablets contain Lamivudine. They contain not less than 90.0 % and not more than 110.0 % of the amount of lamivudine, $C_8H_{11}N_3O_3S$ stated on the label.

Identity tests
Either tests A and C, or tests B and C, or test D alone may be applied.

A. Carry out test A.1. or, where UV detection is not available, test A.2.

A.1. Carry out the test as described under 1.14.1 Thin-layer chromatography*, using silica gel R6 as the coating substance and a mixture of 67 volumes of dichloromethane R, 20 volumes of acetonitrile R, 10 volumes of methanol R and 3 volumes of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 10 µl of each of the following 2 solutions. For solution (A), shake a quantity of the powdered tablets containing about 50 mg of Lamivudine with 50 ml of methanol R, filter, and use the filtrate. For solution (B), use 1.0 mg of lamivudine RS per ml of methanol. After removing the plate from the chromatographic chamber, allow it to dry in a current of cool air, and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity to that obtained with solution B.

A.2. Carry out the test as described under 1.14.1 Thin-layer chromatography*, using silica gel R5 as the coating substance and a mixture of 67 volumes of dichloromethane R, 20 volumes of acetonitrile R, 10 volumes of methanol R and 3 volumes ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 10 ìl of each of the following 2 solutions. For solution (A), shake a quantity of the powdered tablets containing about 50 mg of lamivudine with 50 ml of methanol R, filter, and use the filtrate. For solution (B), use 1.0 mg of lamivudine RS per ml of methanol. After removing the plate from the chromatographic chamber, allow it to dry in a current of cool air. Spray with vanillin/sulfuric acid TS1. Heat the plate for a few minutes at 120 °C. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance, and intensity to that obtained with solution B.

B. See the test described below under Assay A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that obtained with solution (2).

C. The absorption spectrum of the final solution prepared for assay method B, when observed between 210 nm and 300 nm, exhibits one maximum at about 280 nm; the specific absorbance ($A^{1\%}$1cm) is between 577 to 637.

D. To a quantity of the powdered tablets containing 50 mg of Lamivudine add 20 ml of methanol R, shake to dissolve, and filter. Evaporate the filtrate in a stream of nitrogen and, using the test residue thus obtained, carry out the examination as described under 1.7 spectrophotometry in

** Refers to The International Pharmacopoeia*

the infrared region*. The infrared absorption spectrum is concordant with the spectrum obtained from lamivudine RS or with the reference spectrum of lamivudine.

If the spectra thus obtained are not concordant, repeat the test using the test residue and the residue obtained by dissolving lamivudine RS in methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from lamivudine RS.

Related substances
Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with base deactivated particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm). (Hypersil® BDS C18 is suitable.) As the mobile phase, use a mixture of 5 volumes of methanol R and 95 volumes of buffer pH 3.8 (a 1.9 g/l solution of ammonium acetate R, previously adjusted to pH 3.8 with glacial acetic acid R).

Prepare the following solutions. For solution (1), weigh and powder 20 tablets. To a quantity of the powder containing about 50 mg of Lamivudine, add 60 ml of mobile phase and dissolve using an ultrasonic bath if necessary. Dilute to 100 ml with mobile phase. Filter and use the filtrate. For solution (2), dilute 1.0 ml of solution (1) to 100 ml with the mobile phase and then dilute 1.0 ml of this solution to 10 ml.

For the system suitability test: prepare solution (3) in the mobile phase containing about 10 ?g of impurity B RS and 200 µg of lamivudine RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of about 277 nm. Maintain the temperature of the column at 35 ˚C. Inject separately 20 µl each of solutions (1), (2) and (3). Record the chromatograms for about 3 times the retention time of lamivudine in solution (2). The test is not valid unless in the chromatogram obtained with solution (3) the resolution factor between the peaks due to lamivudine and impurity B is greater than 1.5.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). In the chromatogram obtained with solution (1), the area of any peak, other than the principal peak, is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3 %); the area of not more than one such peak is greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2 %)and the area of Not more than two such peaks is greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1 %). The sum of the areas of all peaks, other than the principal peak, is not greater than 6 times the area of the principal peak obtained with solution (2) (0.6 %). Disregard any peak with an area less than 0.5 times the area of the principal peak obtained with solution (2) (0.05 %).

Either test A or B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography*, using the conditions given above under Related substances*. Prepare the following solutions in the mobile phase. For solution (1), weigh and powder 20 tablets. To a quantity of the powder containing about 50 mg of Lamivudine, add 60 ml of mobile phase and dissolve using an ultrasonic bath if necessary. Dilute to 100 ml with mobile phase. Filter a portion of this solution through a 0.45 ìm filter, discarding the first few ml of the filtrate. Dilute 10 ml of the filtrate to 25 ml with mobile phase. For solution (2), use 0.2 mg of lamivudine RS per ml.

Inject separately 20 µl of solution (2) in six replicate injections in the chromatographic system. The assay is not valid unless the relative standard deviation for the peak area of lamivudine is less than 2.0 %.

** Refers to The International Pharmacopoeia*

Inject alternately 20 µl each of solutions (1) and (2).

Measure the areas of the peaks responses of lamivudine obtained in the chromatograms of solutions (1) and (2). Calculate the percentage content of lamivudine, $C_8H_{11}N_3O_3S$.

B. Weigh and powder 20 tablets. Transfer a quantity of the powder containing about 50 mg of Lamivudine, accurately weighed, to a 500 ml volumetric flask. Add about 400 ml of water and dissolve using an ultrasonic bath if necessary. Make up to volume with water. Filter a portion of this solution through a 0.45 ìm filter, discarding the first few ml of the filtrate. Dilute 5 ml of this solution to 50 ml with sulfuric acid (0.1 mol/l) VS. Measure the absorbance of this solution in a 1 cm layer at the maximum about 280 nm against a solvent cell containing the blank. For the blank, use a solution prepared by diluting 5 ml of water with 50 ml of sulfuric acid (0.1 mol/l) VS.

Calculate the percentage content of lamivudine, $C_8H_{11}N_3O_3S$ using the absorptivity value of 60.7 ($A^{1\%}$1cm = 607).

Zidovudine and lamivudine tablets

Draft proposal for The International Pharmacopoeia (May 2006). Please address any comments you may have to: Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: kopps@who.int and rabouhansm@ who.int.

Category. Antiretroviral (nucleoside reverse transcriptase inhibitor).

Storage. Zidovudine and Lamivudine tablets should be kept in a tightly closed container, protected from light.

Additional information. Strengths in the current WHO Model List of Essential Drugs: 300 mg Zidovudine and 150 mg Lamivudine. The tablets may be uncoated or coated.

Requirements

Comply with the monograph for “Tablets”* .

Definition. Zidovudine and lamivudine tablets contain zidovudine and lamivudine. They contain not less than 90.0 % and not more than 110.0 % of the amounts of zidovudine ($C_{10}H_{13}N_5O_4$) and lamivudine ($C_8H_{11}N_3O_3S$) stated on the label.

Identity tests

A. Carry out test A.1. or, where UV detection is not available, test A.2.

A.1. Carry out the test as described under 1.14.1 Thin-layer chromatography*, using silica gel R6 as the coating substance and a mixture of 90 volumes of dichloromethane R, 10 volumes of methanol R and 3 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 µl of each of the following 2 solutions. For solution (A), shake a quantity of the powdered tablets equivalent to about 50 mg of Lamivudine (about 100 mg of Zidovudine) with 50 ml of methanol R, filter, and use the filtrate. For solution (B), use 2.0 mg of zidovudine RS and 1.0 mg of lamivudine RS per ml of methanol. After removing the plate from the chromatographic chamber, allow it to dry in a current of cool air, and examine the chromatogram in ultraviolet light (254 nm).

** Refers to The International Pharmacopoeia*

The two principal spots obtained with solution A correspond in position, appearance, and intensity with those obtained with solution B.

A.2. Carry out the test as described under 1.14.1 Thin-layer chromatography*, using silica gel R5 as the coating substance and a mixture of 90 volumes of dichloromethane R, 10 volumes of methanol R and 3 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 µl of each of the following 2 solutions. For solution (A), shake a quantity of the powdered tablets equivalent to about 50 mg of Lamivudine (about 100 mg of Zidovudine) with 50 ml of methanol R, filter, and use the filtrate. For solution (B), use 2.0 mg of zidovudine RS and 1.0 mg of lamivudine RS per ml of methanol. After removing the plate from the chromatographic chamber, allow it to dry in a current of cool air. Dip the plate in dilute basic potassium permanganate (1 g/l) TS. Examine the chromatogram in daylight.

The two principal spots obtained with solution A correspond in position, appearance, and intensity with those obtained with solution B.

B. See the test described below under assay. The retention times of the principal peaks in the chromatogram obtained from solution (1) of assay are similar to those obtained from solution (2) of assay.

[Note from Secretariat: The possibility of additional tests for Identity is under investigation.]

Related Substances
Carry out the test as described under 1.14.4 High-performance liquid chromatography*, using a stainless steel column (25 cm x 4.6 mm) packed with base deactivated particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm) . Use a mixture of 5 volumes of methanol R and 95 volumes of buffer pH 3.8 (a 1.9 g/l solution of ammonium acetate R, previously adjusted to pH 3.8 with glacial acetic acid R) as the mobile phase A. Use 100% methanol as mobile phase B.

For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powder containing about 100 mg of Zidovudine (about 50 mg of Lamivudine) into a 100 ml volumetric flask. Add about 50 ml of mobile phase A and dissolve by sonicating for 15 minutes. Dilute to volume with the same solvent and mix. Filter through a 0.45 µm filter, discarding the first few ml of the filtered solution. For solution (2), dissolve 2 mg of thymine R in 10 ml of methanol R. Then dilute 2 ml to 20 ml with the mobile phase A. For solution (3), dissolve 1 mg of zidovudine impurity B RS (3'-chloro-3'-deoxythymidine) in 10 ml of methanol R. Then dilute 2 ml to 20 ml with the mobile phase A. For solution (4), dilute 1 ml of solution (1) to 100 ml with mobile phase A.

For the system suitability test: prepare solution (5) in mobile phase A containing about 10 µg per ml of lamivudine impurity B RS, 200 µg per ml of lamivudine RS, 400 µg per ml of zidovudine RS and 10 µg per ml of zidovudine impurity B RS.

Use the following gradient elution:

Time (minutes)	% A	% B
0 – 30	100	0
30 – 40 (linear gradient)	80	20
40 – 45 (hold)	80	20
45 – 55 (linear gradient)	100	0

** Refers to The International Pharmacopoeia*

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 270 nm.

Inject separately 20 µl each of solutions (1), (2), (3), (4) and (5).

The test is not valid unless in the chromatogram obtained with solution (5), the resolution between lamivudine (retention time about 9 minutes) and lamivudine impurity B (relative retention time is about 0.92 with reference to lamivudine) is greater than 1.5 and the resolution between zidovudine (retention time about 42 minutes) and zidovudine impurity B (relative retention time is about 1.03 with reference to zidovudine) is greater than 2.0.

In the chromatogram obtained with solution (1), the area of any peak corresponding to the impurity with a relative retention time of about 0.40 with respect to lamivudine is not greater than 0.3 times the area of the lamivudine peak in the chromatogram obtained with solution (4) (0.3 %). The area of any peak corresponding to the impurity with a relative retention time of about 0.92 with respect to lamivudine is not greater than 0.2 times the area of the lamivudine peak in the chromatogram obtained with solution (4) (0.2 %). The area of any peak corresponding to thymine is not greater than the area of the peak in the chromatogram obtained with solution (2) (2% with respect to zidovudine). The area of any peak corresponding to 3'-chloro-3'-deoxythymidine is not greater than the area of the peak in the chromatogram obtained with solution (3) (1 % with respect to zidovudine).

Assay

Carry out the test as described under 1.14.4 High-performance liquid chromatography*, using the conditions given above under Related Substances*. For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powder containing about 300 mg of Zidovudine (about 150 mg of Lamivudine) into a 100 ml volumetric flask. Add about 50 ml of mobile phase A and dissolve by sonicating for 15 minutes. Dilute to volume with the same solvent and mix. Filter through a 0.45 µm filter, discarding the first few ml of the filtered solution. Dilute 5 ml of the filtrate to 50 ml with the same solvent. For solution (2), prepare a 0.3 mg/ml solution of zidovudine RS and 0.15 mg/ml of lamivudine RS in mobile phase A.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 270 nm.

Inject separately 20 µl of solution (2) in six replicate injections in the chromatographic system. The assay is not valid unless the relative standard deviation for the peak area of both zidovudine and lamivudine is less than 2.0 %.

Inject alternately 20 µl each of solutions (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the percentage content of zidovudine ($C_{10}H_{13}N_5O_4$) and lamivudine ($C_8H_{11}N_3O_3S$).

** Refers to The International Pharmacopoeia*