WHO Drug Information

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Rational Use of Drugs

Prescribing information in 26 countries

Pharmaceutical products approved for marketing are generally accompanied by information targeted to health care prescribers and patients. The International Comparative Study on Drug Information (ICSODI) Collaborative Group has recently published an article in the *European Journal of Clinical Pharmacology* which documents the variability of written drug information in and within countries concerning the indications, side effects and cautions of three selected drugs: ciprofloxacin, fluoxetine and nifedipine. An original method to measure the degree of information agreement among different written materials, such as summaries of product characteristics, package inserts and data sheets, and a widely accepted reference text was developed (1).

Published studies addressing drug information in general (2–5) and readability of patient information materials (6–8) are available, but very little specifically address the issue of documenting differences in key aspects of drug information among different countries for the same drugs (9).

The selected drugs figured among the top thirty in terms of global sales in 2000 (10), and covered three therapeutic areas of high worldwide relevance in terms of mortality and morbidity (11).

A total of 483 written materials were obtained from 26 countries and analysed. Four variables: indications, dosage range in adults, side effects, and cautions were selected and a checklist of items was created using the British National Formulary as a reference text (12). The BNF was chosen because it is a complete, independent, and practice-oriented source of information and is widely used by professionals around the world, being easy to obtain and inexpensive.

Materials collected from each country, drug, and variable were compared with a checklist (see page 146). An indicator for the proportion of agreement was developed. The indicator was called “degree of information agreement” and was based on indications, side effects, and cautions for each country and drug. The proportion of checklist items found in the materials was calculated against the total number of relevant checklist items. The mean and confidence interval for the proportions were then calculated.

The same checklist and methodological approach used in the inter-country evaluation was applied to comparators among materials collected from each individual country.

Baseline characteristics of evaluated materials (26 countries)

		ciprofloxacin (500 mg)	**fluoxetine** (20 mg)	**nifedipine** (10–20 mg)
Companies (No.)		5 different (Bayer in 22 countries)	6 different (Ely Lilly in 21 countries)	7 different (Bayer in 20 countries)
Year of marketing authorization	Range	1987–1999	1987–2000	1976–1999
	Median	1994	1992	1991
Approved material	Yes	14	18	18
	No	12	8	8

BNF-derived checklist for assessing agreement of drug information material

	ciprofloxacin (500 mg)	fluoxetine (20 mg)	nifedipine (20 mg)
Indications	respiratory and urinary tract infections, chronic prostatitis, gonorrhea, pseudomonal lower respiratory tract infection in cystic fibrosis, gastro-intestinal infection (including typhoid fever), septicaemia caused by sensitive organisms, surgical prophylaxis, corneal ulcers, skin and soft-tissue infections	depressive illness, bulimia nervosa, obsessive-compulsive disorder, premenstrual dysphoric disorder	prophylaxis of angina, hypertension, Raynaud phenomenon
Dose (oral, daily, adults)	500–1500 mg	20–60 mg	15–80 mg
Side effects	nausea, diarrhea, vomiting, abdominal pain, jaundice, hepatitis with necrosis, headache, restlessness, Stevens Johnson Syndrome, haemorrhagic bullae, toxic epidermal necrolysis, increase in blood urea and creatinine, hepatic dysfunction (increased serum concentrations of AST and ALT), renal failure, convulsions, hypersensitivity reactions, tendon inflammation and damage	hypersensitivity reactions (angioedema, urticaria, anaphylaxis, pharyngitis, pulmonary inflammation or fibrosis, arthralgia, myalgia, serum sickness), nausea, vomiting, dyspepsia, abdominal pain, diarrhea, constipation, sexual dysfunction, sweating, dry mouth, tremor, nervousness, insomnia, anxiety, headache, lightheadedness, dizziness, suicidal ideation, anorexia with weight loss, movement disorders and dyskinesia, fever, anaemia, convulsion, neuroleptic malignant syndrome-like event, aplastic cerebrovascular accident, eosinophilic pneumonia, gastrointestinal haemorrhage, pancreatitis, pancytopenia, thrombocytopenia, thrombocytopenic purpura, violent behaviour	headache, flushing, dizziness, gravitational edema, exaggerated fall in blood pressure and reflex tachycardia which may lead to myocardial ischaemia, or cerebrovascular ischaemia (short-acting preparation), nausea
Cautions	pregnancy, breast-feeding, children and adolescents, photosensitivity, renal impairment, history of epilepsy, avoid excessive alkalinity of urine, G6PD deficiency, myastenia gravis	diabetes mellitus, epilepsy, hepatic and renal impairment, pregnancy, breast-feeding, concurrent electroconvulsive therapy, cardiac disease, history of bleeding disorders, skilled tasks (impairment), avoid abrupt withdrawal, history of mania, angle closure glycoma	advanced aortic stenosis, myocardial infarction within 1 month, unstable or acute attacks of angina, porphyria, severe hypotension, pregnancy, heart failure, breast-feeding , hepatic impairment, diabetes mellitus, ischaemic pain, avoid grapefruit juice

A comparison was made between the information stated in the BNF and that found in the materials collected. Out of 26 countries, 11 had information that matched BNF indications for nifedipine. Only materials from Colombia and the UK listed all the indications included in the BNF for ciprofloxacin, and those from Canada, Estonia and the UK for fluoxetine. Concerning ciprofloxacin, materials from 3 countries are in disagreement with the dose range recommended by the BNF. This disagreement involved a total of 7 countries for nifedipine and 9 for fluoxetine, i.e. over one-third of the sample. None of the materials from the various countries reported all major side effects listed in the BNF for ciprofloxacin and fluoxetine.

Concerning nifedipine, only materials from Spain were found to report all the BNF side effects, while materials from Colombia did not report any of the 7 major side effects included in the BNF. Again, none of the materials from any of the countries report all the cautions included in the BNF. The findings of this study include extremes such as the presence of 1 caution statement out of the 19 listed in the BNF for ciprofloxacin in the Philippines, 1 out of 11 for fluoxetine in Argentina, and 3 out of 12 for nifedipine in Mozambique and Poland.

What did the analysis show?

Looking at inter-country comparisons, the degree of information agreement is surprisingly low for drugs that are routinely used in large numbers of patients. The disparity of dose ranges recommended by the different sources is especially surprising. Theoretically, prescribing information is based on the assessment of clinical studies and post marketing surveillance activities. In the majority of the cases studied, the materials collected were related to products of the same mother company thus leading to the assumption that the same basic facts should have been used to make the decisions concerning indications, dosage, side effects, and cautions. However, the results show that prescribers and patients are recommended substantially different things in different countries and this may be due to the fact that not all national authorities can conduct a full and systematic assessment of available worldwide data concerning clinical studies and drug monitoring data before approving prescribing information materials.

If intra-country comparisons are examined, the picture becomes even more difficult to understand: why should products have different indications, dosages, side effects and cautions simply because they have a different brand name?

While a plausible explanation cannot be offered for the differences found, it is possible that the implications at national level can be serious for patients and for those engaged in activities aimed at ensuring rational drug use. These implications can also involve communication problems between prescribers, regulatory authorities, companies, and patients. At the international level, there can be serious implications for travellers, or for health workers comparing drug utilization or developing therapeutic guidelines.

In the case of safety information, this was often presented as a list with no frequency indications or any specific guidance for prescribers or patients. Patients presented with such a list of side effects may be reluctant to continue taking a drug. The conclusion is that a list lacking practical guidance is not particularly useful to prescribers or patients. It is urgent for companies and regulatory authorities to understand that correctly presented safety information will assist in decision-making and can speed up identification of adverse reactions.

Responsibility for approving drug information materials lies with national regulatory authorities. Their task is difficult, especially when resources are limited and companies submit different materials in different countries. An effort should be made to identify sources of independent drug information that can be used as a complement to documentation submitted for approval thereby removing contradictory statements on drug information materials that have no reason to be different. Further training and continued education aimed at drug regulatory officials could play a role. Finally, measures to harmonize information materials at the national level, such as requiring the use of core information for pharmaceutically-equivalent products, should be implemented.

References

1. The International Comparative Study on Drug Information (ICSODI) Collaborative Group. Prescribing information in 26 countries: a comparative study. *European Journal of Clinical Pharmacology*, Published online 21 May 2003. http://www.springer.com

2. Curran, C.F. A progress report: Drug information from 1970 to 2000. *Drug Information Journal*, **34**(4):1355–1363 (2000).

3. Garattini, S. How to improve medical information on drugs. *Lancet*, **352**:151–152 (1998).

4. Mindell, J., Kemp, T. Only two-fifths of advertisements cited published, peer reviewed references. *British Medical Journal*, **315**: 1622 (1997).

5. Stryer, D., Bero, L.A. Characteristics of materials distributed by drug companies: An evaluation of appropriateness. *Journal of Internal Medicine,* **11**(10): 575–583 (1996).

6. Bradley, B., Singleton, M., Li Wan Po, A. Readability of patient information leaflets on over-the-counter (OTC) medicines. *Journal of Clinical Pharmacology and Therapeutics*, **19**: 7–15 (1994).

7. Holt, G.A., Dorcheus, L., Hall, E.L. et al. Patient interpretation of label instructions. *American Pharmacy*, **NS32**: 58–62 (1992).

8. Gibbs, S., Waters, W.E., George, F.C. The benefits of prescription information leaflets (2). *British Journal of Clinical Pharmacology,* **28**: 345–351 (1989).

9. Dikshit, R.K., Dikshit, N. Commercial source of drug information: comparison between the UK and India. *British Medical Journal*, **309**: 990–991 (1994).

10. IMS World Review Report. IMS, USA.

11. World Health Organization. World Health Report 2002. Statistical Information System. http://www.who.int/whosis/menu.cfm.

12. The British Medical Association and the Royal Pharmaceutical Society of Great Britain. *British National Formulary*. London, UK; 2000.

Safety and Efficacy Issues

Virologic non-response in HIV drugs

A high rate of early virologic non-response has been observed in a clinical study of therapy-naïve adults receiving once-daily three-drug combination therapy with lamivudine (Epivir®), abacavir (Ziagen®) and tenofovir (Viread™) (1).

Based on these results:

- Abacavir and lamivudine in combination with tenofovir should not be used as a triple antiretroviral therapy when considering a new treatment regimen for naive or pre-treated patients;
- Any patient currently controlled on therapy with this combination should be closely monitored and considered for modification of therapy; and
- Any usage of this triple combination with other antiretroviral agents should be closely monitored for signs of treatment failure.

ESS30009 is a randomized, open-label, multicentre study on the safety and efficacy of efavirenz (EFV) versus tenofovir (TDF) when administered in combination with an investigational abacavir(ABC)/lamivudine (3TC) fixed-dose combination tablet as a once-daily regimen in antiretroviral-naïve HIV-1 infected adults.

Shortly after initiation of this study the sponsor, GlaxoSmithKline, received reports from investigators of poor efficacy in patients receiving TDF+ 3TC+ABC. An urgent, unplanned interim analysis was conducted to assess virologic non-response. Results are shown in the table below. The precise nature of any interaction leading to non-response in this study is not known. Preliminary genotypes of viral isolates from 14 patients with non-response taking the TDF+3TC+ABC regimen have shown all 14 isolates had the M184V mutation in HIV reverse transcriptase. In addition, 8 of the 14 (57%) isolates also had the K65R mutation.

On review of these results, GSK promptly informed all participating clinical investigators and terminated the TDF+3TC+ABC arm in this study. Clinical investigators are working with patients to change therapy based on genotype and clinical judgement. The once daily EFV+3TC+ABC arm performed well and continues unchanged in this clinical study.

In addition to study ESS30009, a pilot study (2) has provided data in 20 patients receiving TDF+3TC+ ABC once daily for initial therapy. A high rate of virologic non-response was also documented.

References

1. GlaxoSmithKline letter to health care providers published on www.FDA.gov/medwatch.

2. Farthing, et al. 2nd annual meeting of the International AIDS Society, July 2003, Paris, France.

3. Informative Note 2003/09. Spanish medicines Agency, 31 July 2003 http://www.agemed.es.

	Number (%) of patients meeting the definition of virologic non-response	
	TDF + 3TC + ABC	**EFV + 3TC + ABC**
HIV-1 RNA data for subjects on therapy for > or equal to 8 weeks	50 / 102 (49%)	5 / 92 (5%)
HIV-1 RNA data for subjects on therapy for > or equal to 12 weeks	30 / 63 (48%)	3 / 62 (5%)

Hyponatraemia with SSRIs

The Australian Adverse Reactions Advisory Committee (ADRAC) has received a total of 311 reports of hyponatraemia involving serotonin selective reuptake inhibitors (SSRIs) and venlafaxine. In 67 of these reports, it was indicated that the patient had the syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) although serum and/or urine osmolality results were not included in every case (1). As a group, the SSRIs account for about one-quarter of all reports of hyponatraemia received by ADRAC, and are second to diuretics as the group most commonly associated with hyponatraemia.

Reports of hyponatraemia with SSRIs and venlafaxine

Drug	Total reports	Reports of hyponatraemia
Citalopram	388	35
Fluoxetine	1148	50
Fluvoxamine	142	3
Paroxetine	1587	46
Sertraline	4503	130
Venlafaxine	695	47

In more than two-thirds of the 311 reports, the SSRI was the only suspected drug and three-quarters of the reports involved females. A small proportion (14%) identified concurrent use of a diuretic. The median patient age was 77 years (range 13 to 99); about 85% were older than 60 years. Onset was usually within the first month of treatment. In many of the reports hyponatraemia was the sole abnormality reported, with the median serum sodium nadir at 120 (range 113 to 133) mmol/L. Other reports listed neuropsychological symptoms such as confusion, convulsions, fatigue, delirium, syncope, somnolence, agitation, dizziness and hallucinations. Some patients experienced other behavioural changes such as aggressive reactions, personality disorders or depersonalization. Changes in pulse or blood pressure occasionally occurred.

In about two-thirds of cases, full recovery followed withdrawal of the SSRI and fluid restriction. Three cases had a fatal outcome related to hyponatraemia. Other patients had not recovered or the outcome was unknown at the time of reporting. The pattern of ADRAC reports is consistent with published findings suggesting that hyponatraemia with SSRIs is more frequent in the elderly, particularly females, and onset is mostly during the first 30 days after commencing an SSRI (2). SIADH appears to be part of the mechanism of hyponatraemia with the SSRIs, and inhibition of serotonin reuptake may be associated with a central increase in ADH release and hence induction of SIADH (3).

A recent Australian study of elderly psychiatric patients found that use of an SSRI or venlafaxine was associated with a 3.5-fold increase in the risk of hyponatraemia after controlling for age, sex, depression status, use of other drugs associated with hyponatraemia and seriousness of physical disease (4).

Neuropsychological symptoms developing in the first month of SSRI or venlafaxine use should prompt measurement of serum electrolytes. Elderly females and patients taking diuretics are at added risk.

Extracted from Australian Adverse Drug Reaction Bulletin, Volume 22, Number 3, 2003.

References

1. ADRAC. Selective serotonin reuptake inhibitors and SIADH. *Medical Journal of Australia*, **164**: 562 (1996).

2. Liu, B., Mittmann, N., Knowles, S. et al. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone associated with the use of selective serotonin reuptake inhibitors. *Canadian Medical Association Journal*, **155** (5): 519–527 (1996).

3. Fisher, A., Davis, M., Croft-Baker, J. et al. Citalopram-induced severe hyponatraemia with coma and seizure. *Adverse Drug Reaction and Toxicology Review*, **21**: 179–187 (2002).

4. Kirby, D., Harrigan, S., Ames, D. Hyponatraemia in elderly psychiatric patients treated with selective serotonin reuptake inhibitors and venlafaxine. *International Journal of Geriatric Psychiatry*, **17**: 231–237 (2002).

Salmeterol labelling changes

The Food and Drug Administration (FDA) has announced new safety information and warnings to be added to the labelling for drug products containing the long-acting bronchodilator, salmeterol, used to treat asthma and chronic obstructive pulmonary disease (COPD). A small but significant increased risk of life-threatening asthma episodes or asthma-related deaths have been observed.

On 23 January 2003, FDA released a talk paper announcing the preliminary results of an interim analysis of the Salmeterol Multicentre Asthma Research Trial (SMART), which compared the effects of salmeterol to placebo in patients with asthma for a period of 28 weeks. The primary endpoint was the occurrence of either respiratory-related death or a respiratory-related life-threatening experience (e.g., requirement for mechanical ventilation). Secondary endpoints included all-cause death, asthma-related death, and asthma-related death or life-threatening experience.

Although the study was intended to enrol 60 000 patients, the study was stopped by the sponsor after review of the results of a planned interim analysis after approximately half of the intended number of patients were enrolled. The analysis includes 13 174 patients treated with Serevent®, and 13 179 patients treated with placebo. The analysis showed no significant difference between treatment groups for the primary endpoint, however, a higher number of asthma-related deaths (13 vs. 4), and a higher number of asthma-related deaths or life-threatening experiences (36 vs. 23) were observed in the Serevent® group compared to placebo.

The SMART study was not designed to analyse differences in outcome based on demographic characteristics but post-hoc subgroup analyses based on race and ethnicity were conducted. These analyses showed no increase in respiratory- or asthma-related events among Caucasian patients. For African-American patients there was a statistically significant increase in primary events (respiratory-related death of life-threatening experience) in the Serevent® group (20 vs. 7). In addition, the occurrence of asthma-related death (8 vs. 1) and asthma-related death or life-threatening experience (19 vs. 4) was statistically significantly greater in African-American patients compared to placebo.

The Food and Drug Administration (FDA) emphasizes that based on available data the benefits of treatment with salmeterol in patients with asthma and COPD continue to outweigh the potential risks when used according to the instructions contained in the product labelling. Patients are advised not to stop taking products without first consulting their physicians.

Reference: *FDA Talk Paper*, T03–62, 14 August 2003

Pregnancy during depot medroxyprogesterone use

The Australian Adverse Reactions Advisory Committee (ADRAC) has received 27 reports of women becoming pregnant despite using depot medroxyprogesterone products (Depo-Provera®, Depo-Ralovera®) for contraception. In ten of the cases, the woman was confirmed as becoming pregnant 2–10 weeks after administration of the drug. An interaction with carbamazepine may have been a factor in two of these cases. In another nine cases, the injections were given late or at borderline times.

These depot progesterone contraceptives have a high level of efficacy (1). However, prescribers and other health care professionals who administer these drugs need to avoid the following situations which contribute to the risk of contraceptive failure:

- Incorrect timing of the injection — injections must be commenced during the first five days after the onset of a normal menstrual period, within five days postpartum if not breast-feeding or, if breast-feeding, at six weeks post-partum, after having excluded pregnancy. Injections are given at 3-monthly intervals, no more than 14 weeks apart. If the interval is greater than 14 weeks, a pregnancy test should be conducted prior to administration.

- Failure to properly suspend the microcrystals by not adequately shaking the vial. Storing vials on their side may allow the microcrystals to cake and fail to suspend when shaken.

- Failure to give the full dose — inadequate drawing up or full dose not injected.

- Incorrect injection technique with deposition of the suspension in tissues superficial to the muscles.

- Incorrect drug being administered — there has been one case of Depo-Medrol® being used instead of Depo-Provera®.

Extracted from Australian Adverse Drug Reaction Bulletin, Volume 22, Number 3, 2003.

Reference: Borgatta, L., Murthy, A., Chuang, C. et al. Pregnancies diagnosed during Depo-Provera® use. *Contraception*, **66**: 169–172 (2002).

Etonogestrel and vaginal bleeding

Since August 2001, the Australian Adverse Reactions Advisory Committee (ADRAC) has received 130 adverse reaction reports for Implanon® (subdermal etonogestrel contraceptive implant), including 37 reports of vaginal bleeding, most of which described prolonged bleeding (duration 2–26 weeks; median 8 weeks). The bleeding generally started soon after insertion, but the time to onset was up to 16 weeks. Thirty-three of the 37 patients required implant removal. One patient was hospitalized, and transfused 4 units of packed red blood cells.

In a published 3-year study, 2.8% of patients experienced heavy or prolonged bleeding with Implanon® (1). Unacceptable vaginal bleeding may occasionally occur and often requires implant removal.

Extracted from Australian Adverse Drug Reaction Bulletin, Volume 22, Number 3, 2003.

Reference: Croxatto, H.B. Clinical profile of Implanon®: a single-rod etonogestrel contraceptive implant. *European Journal of Contraception and Reproductive Health Care*, **5**(Suppl 2): 21–28 (2000).

Hepatic reactions with minocycline

Minocycline is an effective long-term treatment for severe acne, but is associated with serious adverse reactions, including rare cases of hepatic dysfunction. In one study, the incidence of hepatic reactions in new users was one case/10 000 person-months (1).

ADRAC has received 42 reports of hepatic reactions with minocycline including 21 of hepatitis. It was the only drug taken by most of these patients, and was used for acne by 28. Fifteen patients were under 21 years of age. Where liver enzyme results were provided, they showed a hepatocellular pattern (12) more often than a cholestatic (3) or mixed picture (2). Time to onset was provided in 13 reports and suggested that cholestatic reactions occurred earlier (= 4 weeks) than hepatocellular damage (usually after months or years). Of the 42 cases, 25 had recovered by the time of reporting, usually in less than 12 weeks. None of the patients died or required liver transplantation.

A published case series suggests that hepatic reactions with minocycline may present either with features of a hypersensitivity syndrome (onset within 35 days) or resemble autoimmune chronic active hepatitis (onset after months or years) (2). Despite well-documented reports, no ADRAC cases conformed to the criteria for a hypersensitivity syndrome. However, five reports were suggestive of an autoimmune reaction. All cases had antinuclear antibodies, and one had other features of lupus erythematosus. A time to onset of 11 or 12 months was specified in two cases.

Other serious adverse reactions associated with minocycline include CNS effects, skin discolouration and benign intracranial hypertension. Prescribers are particularly advised to note that hepatitis developing in a patient on long-term minocycline may be indistinguishable from autoimmune hepatitis both serologically and histologically. Discontinuation of minocycline usually results in complete recovery.

Extracted from Australian Adverse Drug Reaction Bulletin, Volume 22, Number 3, 2003.

References

1. Seaman, H.E., Lawrenson, R.A., Williams, T.J. et al. The risk of liver damage associated with minocycline: a comparative study. *Journal of Clinical Pharmacology*, **41**(8): 852–860 (2001).

2. Lawrenson, R.A., Seaman, H.E., Sundstrom, A. et al. Liver damage associated with minocycline use in acne: a systematic review of the published literature and pharmacovigilance data. *Drug Safety*, **23**: 333–349 (2000).

Hepatobiliary reactions with the newer antidepressants

Health Canada continues to monitor suspected hepatobiliary adverse reactions (ARs) associated with the newer antidepressants that exert an effect on serotonin neurotransmission. These include citalopram (Celexa®), fluoxetine (Prozac®), fluvoxamine (Luvox®), mirtazapine (Remeron®), nefazodone (Serzone-5HT$_2$®), paroxetine (Paxil®), sertraline (Zoloft®), trazodone (Desyrel®) and venlafaxine (Effexor®). Reports of suspected hepatobiliary ARs associated with these antidepressants were submitted to Health Canada from the time of marketing to July 2002.

From the data available, no fatal outcomes were reported for hepatobiliary ARs associated with these antidepressants. In two reports involving nefazodone, liver transplantation was required. In three other reports involving nefazodone liver transplantation was considered, but the patients' conditions eventually improved after prolonged hospital care. The time of onset of liver injury ranged from 1 to 4 months. None of these five patients had a prior history of liver disease.

The current literature documents several cases of severe hepatic failure associated with nefazodone. The US Food and Drug Administration (FDA) recently included a black-box warning in Serzone® package insert, stating that the reported rate in the United States of liver failure resulting in death or liver transplantation is about 1 case per 250 000–300 000 patient-years of treatment. This rate is about 3-4 times the estimated background rate of liver failure. It is possibly an underestimate of true risk because of underreporting.

At present, there is no way to predict in which patient liver failure is likely to develop. Ordinarily, treatment with nefazodone should not be initiated in patients with active liver disease or with an elevated baseline serum transaminase level. Although it is unclear whether periodic liver function tests can help prevent serious liver injury, it is generally believed that early detection of drug-induced hepatic injury along with immediate discontinuation of the suspected drug enhances the likelihood of recovery.

Mano Murty, Iza Morawiecka, Suniti Sharma. Canadian Adverse Reaction Newsletter, 13(1), January 2003

References

1. Nefazodone: adverse drug reaction profile. *Canadian Adverse Drug Reaction Newsletter*, **6**(2): 2 (1996).

2. Nefazodone (Serzone) and hepatotoxicity. *Canadian Adverse Drug Reaction Newsletter,* **9**(3): 2–3 (1999).

3. Important safety information on nefazodone HCl: severe and serious hepatic events [Dear Healthcare Professional Letter]. Montreal: Bristol-Myers Squibb Canada Inc and Linson Pharma Inc., 20 June 2001.

4. Important safety information on nefazodone HCl: severe and serious hepatic events [Dear Healthcare Professional Letter]. Weston (ON): Apotex Inc., June 2001.

5. Risk of severe liver injury associated with the use of the antidepressant nefazodone [public advisory]. Ottawa: Health Canada; 9 July 2001.

6. Aranda-Michel, J., Koehler, A., Bejarano, P.A., et al. Nefazodone-induced liver failure: report of three cases. *Annals of Internal Medicine*, **130**: 285–288 (1999).

7. Schirren, C.A., Baretton, G. Nefazodone-induced acute liver failure. *American Journal Gastroenterology*, **95**(6):1596–1597 (2000).

8. Carvajal, A., Garcia del Pozo, J. et al. Hepatotoxicity associated with the new antidepressants. *Journal of Clinical Psychiatry*, **63**(2):135–137 (2002).

9. Important drug warning including black box information [Dear Healthcare Practitioner Letter]. New York: Bristol-Myers Squibb, January 2002.

10. Serzone-5HT2, nefazodone hydrochloride tablets [product monograph]. Montreal: Bristol-Myers Squibb Canada Inc., 5 October 2001.

Convulsions with newer-generation antihistamines

Antagonists of histamine H_1 receptors are commonly classified as first-generation or new-generation antihistamines based on their frequent sedating effect at therapeutic doses. The "newer-generation" antihistamines, also known as second- or third-generation antihistamines, include astemizole, cetirizine, desloratadine, fexofenadine, loratadine and terfenadine, and were developed as nonsedating alternatives to the first-generation compounds. The sale of terfenadine and astemizole was stopped in Canada because of associated QT prolongation, which could lead to torsades de pointes or ventricular fibrillation. Loratadine, cetirizine, fexofenadine and desloratadine have been marketed in Canada since 1988, 1991, 1997 and 2002, respectively. Loratadine, fexofenadine and desloratadine are available as nonprescription drugs. Cetirizine is available as both a nonprescription and prescription drug.

Seizures or convulsions have been reported in the literature with some first-generation antihistamines (chlorpheniramine, diphenhydramine, pheniramine and pyribenzamine) as well as with some newer-generation antihistamines (astemizole, cetirizine, fexofenadine, loratadine and terfenadine). According to the US Food and Drug Administration Adverse Event Reporting System (July 1999), convulsions associated with ceti-

rizine, fexofenadine and loratadine accounted for 2.5%, 3.1% and 2.1% respectively of the total adverse events reported with these drugs.

From their respective dates of marketing in Canada to 19 September 2002, Health Canada received 20 reports of suspected convulsive disorders associated with the use of loratadine (9), cetirizine (7) and fexofenadine (4). There have been no reports of suspected convulsive disorders associated with desloratadine at this time. Reports of seizures and convulsions accounted for 3.6%, 1.4% and 0.9% of the total number of adverse reactions (ARs) reported with loratadine, cetirizine and fexofenadine respectively. Fifteen of the 20 cases occurred in patients with a prior history of seizures or in those who used anticonvulsant drugs concomitantly. However, these data must be interpreted with caution, as causality has not been confirmed. It is unclear whether newer-generation antihistamines aggravate the medical condition of patients with a history of seizures or whether they interact with anticonvulsants. Further studies and continued monitoring of these agents regarding their role in causing seizures or convulsions, especially in patients predisposed to convulsive disorders, are required.

Also of note are two reports of patients who apparently took more than the recommended daily dose of the drug. One report involved a 27-year-old woman receiving phenytoin therapy who had been seizure free for over 2 years. She took 3 doses of cetirizine (20 mg each) in 24 hours and experienced a seizure 1+ hours after the third dose. The maximum recommended daily dose of cetirizine is 20 mg. The other report was of a healthy 37-year-old man with no history of seizures who experienced 2 grand mal seizures, 3 hours apart, after 3 days of taking 25 mg of loratadine daily (in the form of 2 tablets of Claritin® and 1 tablet of Claritin Extra®). The patient had also ingested alcohol (+ beer) the night before the seizure. The recommended daily adult dose of loratadine is 10 mg.

Patients should be reminded to read package labels carefully and not to exceed the recommended or maximum daily dose of any therapeutic health product, including nonprescription drugs. Patients should also be made aware that multiple products may contain the same active ingredients and to consult their health care professional for further information.

Pascale Springuel, Duc Vu, Canadian Adverse Reaction Newsletter, 13(1), January 2003

References

1. Ten Eick, A.P., Blumer, J.L., Reed, M.D. Safety of antihistamines in children. *Drug Safety*, **24**(2): 119–147 (2001).

2. Blain, P.G., Lane, R.M. Neurological disorders. In: Davies, D.M., Ferner, R.E., De Glanville, H. eds. *Davies's textbook of adverse drug reactions*. 5th ed. London: Chapman and Hall Medical; 1998. pp. 591–593.

3. Murphy, K., Delanty, N. Drug-induced seizures: general principles in assessment, management and prevention. *CNS Drugs*, **14**(2): 135–146 (2000).

4. Reactine, cetirizine hydrochloride tablets, syrup [product monograph]. Kirkland (QC): Pfizer Canada Inc; 29 September 2000.

5. Claritin, loratadine tablets, rapid dissolve tongue tablets, syrup [product monograph]. Pointe-Claire (QC): Schering Canada Inc, 15 June 2001.

6. Claritin Extra, loratadine and pseudoephedrine repetabs tablets [product monograph]. Pointe-Claire (QC): Schering Canada Inc; 13 March 1998.

Rifampicin and pyrazinamide not to be used for latent tuberculosis infection

The Centers for Disease Control (CDC) has reported severe liver injury in patients treated for latent tuberculosis infection (LTBI) with a daily and twice-weekly 2-month regimen of rifampicin (US: rifampin) with pyrazinamide (RZ). On the basis of these initial reports, CDC has cautioned clinicians in the use of this therapy. To estimate the incidence of RZ-associated severe liver injury CDC collected data from cohorts of patients in the United States who received RZ for the treatment of LTBI. Analysis found high rates of hospitalization and death from liver injury associated with the use of RZ. On the basis of these findings, the American Thoracic Society (ATS) and CDC now recommend that this regimen should generally not be offered to persons with LTBI.

The revised ATS/CDC recommendations are endorsed by the Infectious Diseases Society of America (IDSA). Clinicians are advised to use the recommended alternative regimens for the treatment of LTBI. Rifampicin and pyrazinamide

(PZA) should continue to be administered in multidrug regimens for the treatment of persons with active tuberculosis (TB) disease.

This regimen should generally not be offered to persons with LTBI for either HIV-negative or HIV-infected persons and should never be offered to patients who:

- are concurrently taking other medications associated with liver injury;
- drink excessive amounts of alcohol, even if alcohol use is discontinued during treatment;
- have underlying liver disease; or
- have a history of isoniazid (INH)-associated liver injury.

If the potential benefits of this regimen outweigh the risk for severe liver injury and death associated with it, use of RZ might be considered in carefully selected patients, but only if:

- the preferred or alternative regimens (i.e., 9 months of daily or biweekly INH, 6 months of daily or biweekly INH, or 4 months of daily rifampicin) are judged not likely to be completed and
- oversight by a clinician with expertise in the treatment of LTBI can be provided.

A TB/LTBI expert should be consulted before RZ is offered. In addition, patients should be asked whether they have had liver disease or adverse effects from taking INH or other drugs, informed of potential hepatotoxicity of the RZ regimen, and advised against the concurrent use of potentially hepatotoxic drugs, including over-the-counter drugs such as paracetamol (acetaminophen).

To facilitate periodic clinical assessments of persons taking an RZ regimen (clinicians should dispense no more than a 2-week supply (with a daily PZA dose of <20.0 mg/kg/d [maximum daily PZA dose: 2.0 g], and a twice-weekly dose of <50.0 mg/kg/d [maximum twice-weekly PZA dose: 4.0 g]).

Patients should be reassessed in person by a health-care provider at 2, 4, 6, and 8 weeks of treatment for adherence, tolerance, and adverse effects. The 8-week assessment also should be used to document treatment completion. At each visit, health-care providers who speak the patient's own language should instruct the patient to stop taking RZ immediately and seek medical consultation if abdominal pain, emesis, jaundice, or other symptoms of hepatitis develop. Provider continuity is recommended for optimal monitoring.

For persons taking this regimen, serum aminotransaminases (AT) and bilirubin should be measured at baseline and at 2, 4, 6, and 8 weeks of treatment. Because the majority of these patients had onset of symptoms of liver injury after the fourth week of therapy they should be monitored throughout the entire course of treatment. Use of RZ should be discontinued immediately and not resumed for any of the following findings:

- AT greater than five times the upper limit of normal range in an asymptomatic person,
- AT greater than normal range when accompanied by symptoms of hepatitis, or
- a serum bilirubin concentration greater than the normal range, whether or not symptoms are present.

The risk for progression from LTBI to active TB is increased substantially in persons with HIV infection. Therefore, as recommended previously for the treatment of all persons in whom LTBI is diagnosed, voluntary HIV counselling and testing should be offered routinely.

Recommendations against the use of RZ for treatment of LTBI do not apply to the appropriate use of rifampicin and PZA in multidrug regimens for the treatment of persons with active TB disease.

Reference: CDC. Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampicin and Pyrazinamide for Treatment of Latent Tuberculosis Infection. *Morbidity and Mortality Weekly Report*, **52**: 735–739 (2003).

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.

Individual Drugs

The role of statins in primary prevention

Two important questions regarding statin therapy are:

- What is the overall health impact when statins are prescribed for primary prevention?
- Should the dose of statin be titrated to achieve target lipid levels?

Three new randomized controlled trials (1–3) help answer the first question.

Estimating the overall health impact of statins in primary prevention requires balancing possible benefits and possible harms. The benefit is estimated by combining two cardiovascular serious adverse events known to be reduced by statins in secondary prevention trials: total myocardial infarction (fatal and non-fatal) (5) and total stroke (fatal and non-fatal) (6). The balance between benefit and harm (overall health impact) is estimated by total mortality and total serious adverse events. Serious adverse events include any untoward medical occurrence that results in death, is life threatening, requires hospitalization or prolongation of hospitalization, or results in persistent or significant disability.

PROSPER

Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) (1) studied the effect of pravastatin compared to placebo in two older populations of patients: 56% primary prevention (no past or symptomatic cardiovascular disease) and 44% secondary prevention (past or symptomatic cardiovascular disease) (Table 1). Pravastatin did not reduce total myocardial infarction or total stroke in the primary prevention population, RR 0.94 [0.78 – 1.14], but did so in the secondary prevention population, RR 0.80 [0.68 – 0.94], ARR 4.3%, NNT 23 for 3.2 years. Measures of overall health impact in the combined populations, total mortality and total serious adverse events, were unchanged by pravastatin as compared to placebo, RR 0.98 [0.84 – 1.14] and 1.01 [0.96 – 1.06], respectively.

ALLHAT-LLT

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) (2) was designed to determine whether pravastatin compared with usual care reduces all-cause mortality in older, moderately hypercholesterolaemic, hypertensive patients with at least one additional coronary heart disease risk factor. The published data is for the whole population, 86% of which was primary prevention. Pravastatin did not reduce total myocardial infarction and total stroke, RR 0.91 [0.82 – 1.01]. Pravastatin also did not reduce total mortality, RR 0.99 [0.89 – 1.09]. Total serious adverse events were not reported.

Table 1 (abridged): Characteristics of the 5 major statin primary prevention trials

Trial	Drug Name	Dose mg/day	*N*	Average age (yrs)	% Primary Prevention
PROSPER	pravastatin	40	5804	75	56
ALLHAT-LLT	pravastatin	40	10 355	66	86
ASCOT-LLA	atorvastatin	10	10 305	63	82
AFCAPS	lovastatin	20-40	6605	58	100
WOSCOP	pravastatin	40	6595	55	92

** % reduction in the statin group minus the control group after 1 to 2 years of therapy.*
N = total number of patients in trial

ASCOT-LLA

The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) was designed to assess the benefits of atorvastatin versus placebo in hypertensive patients with average or lower-than-average cholesterol concentrations and at least three other cardiovascular risk factors. The published data is for the whole population, 82% of which was primary prevention. The trial was originally planned for 5 years, but was stopped after a median follow-up of 3.3 years because of a significant reduction in cardiac events. Atorvastatin reduced total myocardial infarction and total stroke, RR 0.82 [0.70 – 0.96], ARR 1.2%, NNT 83. Total mortality was not significantly reduced, RR 0.87 [0.71 – 1.05]. The trial report stated that total serious adverse events did not differ between patients assigned atorvastatin or placebo, but the actual numbers of serious adverse events were not given.

Overall health impact when statins are prescribed for primary prevention

To answer this question we combined the data from the 5 mostly primary prevention trials, the 3 above plus 2 published earlier (Tables 1 and 2). These calculations reflect a population that is 84% primary prevention and 16% secondary prevention. In the pooled data the statins reduced the cardiovascular measures, total myocardial infarction and total stroke by 1.4% as compared to control. This value indicates that 71 mostly primary prevention patients would have to be treated for 3 to 5 years to prevent one such event. This can be compared with the same pooled outcome in 4 large secondary prevention statin trials, ARR 4.8%, NNT 21 for 5 years (4).

In the 2 trials where serious adverse events are reported, the 1.8% absolute reduction in myocardial infarction and stroke should be reflected by a similar absolute reduction in total serious adverse events; myocardial infarction and stroke are, by definition, serious adverse events. However, this is not the case; serious adverse events are similar in the statin group, 44.2%, and the control group, 43.9% (Table 2). This is consistent with the possibility that unrecognized serious adverse events are increased by statin therapy and that the magnitude of the increase is similar to the magnitude of the reduction in cardiovascular serious adverse events in these populations. This hypothesis needs to be tested by analysis of total serious adverse event data in both past and future statin trials. Serious adverse event data is available to trial authors, drug companies and drug regulators. The other measure of overall impact, total mortality, is available in all 5 trials and is not reduced by statin therapy

Conclusions

- If cardiovascular serious adverse events are viewed in isolation, 71 primary prevention patients with cardiovascular risk factors have to be treated with a statin for 3 to 5 years to prevent one myocardial infarction or stroke.
- This cardiovascular benefit is not reflected in 2 measures of overall health impact, total mortality and total serious adverse events. Therefore, statins have not been shown to provide an overall health benefit in primary prevention trials.

Extracted from Therapeutics Letter, Number 48, http://www.ti.bc.ca

Table 2: Meta-analysis of major outcomes from 5 statin primary prevention trials

Outcome	Statin		Control		RR [95% CI]		ARR		NNT (3-5 yr)	
	5 trials	2 trials*	5 trials	2 trials*	5 trials	2 trials*	5 trials	2 trials*	5 trials	2 trials*
Total mortality	6.6	6.1	6.9	6.2	0.95 [0.88-1.02]	0.99 [0.87-1.14]				
Total MI and stroke	7.3	8.0	8.7	9.8	0.84 [0.78-0.90]	0.82 [0.78-0.90]	1.4	1.8	71	56
Total SAEs*		44.2		43.9		1.01 [0.97-1.05]				

** AFCAPS and PROSPER MI = Myocardial Infarction SAEs = Serious Adverse Events RR = Relative Risk. CI = Confidence Interval ARR = Absolute Risk Reduction NNT = Number Needed to Treat to prevent one event.*

Comments from Management of Noncommunicable Diseases (NMC), World Health Organization

The ASCOT-LLA was ended early after an interim analysis showed an outcome in favour of statin treatment. However, the additional benefit to effective lowering of blood pressure by statin therapy is not impressive in absolute terms. The study population was mostly men/white, mean age 63, average of 3.7 risk factors in addition to hypertension. In other words, patients at rather high cardiovascular risk. Further statin treatment lowered total cholesterol by 1.3 mmol and blood pressure was well controlled; both factors contributing to the outcome.

On the other hand, the ALLHAT LLT trial patients had hypertension with at least one cardiovascular risk factor. The difference in total cholesterol between groups during the trial was only around 0.5 mmol/L and the trial failed to show any benefit in all-cause mortality (primary outcome) or in non fatal myocardial infarction and non-fatal coronary heart disease (secondary outcome).

The above findings, and the results of the other studies reiterate:

1. That the safety of statins have to be proven in people with low coronary heart disease risk. However, extremely large trials are required to demonstrate the safety of statins in terms of overall mortality in such subjects.

2. That treatment strategies in primary prevention of cardiovascular disease should depend on global cardiovascular risk assessment rather than on numerical values of individual risk factors.

References

1. Shepherd, J., Blauw, G.J., Murphy, M.B. et al. PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. *Lancet*, **360**: 1623–1630 (2002).

2. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolaemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *Journal of the American Medical Association*, **288**: 2998–3007 (2002).

3. Sever, P.S., Dhalof, B., Poulter, N.R. et al. ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial. *Lancet*, **361**: 1149–1158 (2003).

4. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomized placebo-controlled trial. *Lancet*, **360**: 7–22 (2002).

5. Maron, D.J., Fazio, S., Linton, M.F. Current perspectives on statins. *Circulation*, **101**: 207–213 (2000).

6. Crouse, J.R., Byington, R.P., Furberg, C.D. HMG-CoA reductase inhibitor therapy and stroke risk reduction: an analysis of clinical trials data. [erratum appears in *Atherosclerosis* **140**: 193–194 1998]. *Atherosclerosis*, **138**: 11–24 (1998).

7. Downs, J.R., Clearfield, M., Weis, S., et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *Journal of the American Medical Association,* **279**: 1615–1622 (1998).

8. Shepherd, J., Cobbe, S.M., Ford, I. et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolaemia. *New England Journal of Medicine*, **333**: 1301–1307 (1995).

A strategy to reduce cardiovascular disease by more than 80% ?

Heart attacks, stroke, and other preventable cardiovascular diseases kill or seriously affect many populations. Western diet and lifestyle increase levels of risk factors and their combined effects have made these diseases common. Cardiovascular disease can be avoided or delayed, but the necessary changes to Western diet and lifestyle are not practicable in the short term. Randomized trials show that drugs to lower three risk factors—low density lipoprotein (LDL) cholesterol, blood pressure, and platelet function (with aspirin)—reduce the incidence of ischaemic heart disease (IHD) events and stroke. Evidence that lowering serum homocysteine (with folic acid) reduces the risk of these diseases is largely observational but still compelling.

With this in mind, a meta-analysis has recently been carried out in the United Kingdom (1) to determine the combination of drugs and vitamins to achieve prevention of cardiovascular disease with minimal adverse effects as a single daily polypill (2). The strategy would simultaneously reduce four cardiovascular risk factors: low-

density lipoprotein cholesterol, blood pressure, serum homocysteine, and platelet function, regardless of pretreatment levels.

The following polypill formulations are proposed:

- a statin: e.g. atorvastatin or simvastatin;
- three blood pressure lowering drugs: e.g. a thiazide, beta blocker, and angiotensin converting enzyme (ACE) inhibitor;
- folic acid; and
- aspirin.

The polypill is estimated to reduce IHD events by 88% and stroke by 80%. One-third of people taking this pill from age 55 would therefore benefit — gaining on average about 11 years of life free from an IHD event or stroke. Summing the adverse effects of the components observed in randomized trials showed that the polypill would cause symptoms in 8–15% of people depending on the precise formulation. The authors propose that this strategy could largely prevent heart attacks and stroke if taken by everyone aged 55 and older and everyone with existing cardiovascular disease. It would be acceptably safe and with widespread use would have a greater impact on the prevention of disease in the Western world than any other single intervention.

A large preventive effect would require intervention in everyone at increased risk irrespective of the risk factor levels; intervention on several reversible causal risk factors together; and reducing these risk factors by as much as possible.

A low-cost polypill could use generic components that are no longer subject to patent protection. This formulation does not have the lowest rate of adverse effects, but even if about 10% of people were intolerant of the formulation it would still have considerable public health merit. Those found to be intolerant could be prescribed alternatives to avoid the side effects. Controlled trials of different formulations of the polypill would provide direct estimates of acceptability.

The preventive strategy outlined is radical. But the authors argue that a formulation that prevented all cancer and was safe would undoubtedly be widely used, and one that prevented more than 80% of cardiovascular disease would be even more important because such deaths are more common than cancer deaths. It is also pointed out that in Western society the risk factors are high and everyone is at risk. The diseases they cause are common and often fatal and there is much to gain and little to lose by the widespread use of these drugs. No other preventive method would have so great an impact on public health in the Western world.

Reference:

1. Law, M.R., Wald, N.J., Rudnicka, A.R. Quantifying effect of statins on low density lipoprotein cholesterol ischaemic heart disease, and stroke: systematic review and meta-analysis. *British Medical Journal*, **326**: 1423 (2003).

2. Wald, N.J., Law, M.R. A strategy to reduce cardiovascular disease by more than 80%. *British Medical Journal*, **326**: 1419–1422 (2003).

Aspects of Quality Assurance

Pre-qualification of HIV drugs

The Pilot Procurement, Quality and Sourcing Project for HIV Drugs was created in October 2000 by WHO, UNICEF, UNFPA, and UNAIDS, with support from the World Bank. Its objective is to pre-qualify manufacturers of medicines for HIV (antiretrovirals) and HIV-related illnesses (anti-infectives, anticancer medicines, and pain killers) as suppliers to United Nations and other public sector drug procurement agencies. Medicines for the treatment of HIV infection have been selected because they remain largely inaccessible in those countries that are most affected by HIV/AIDS.

For antiretrovirals, there is currently limited regulatory experience, and well-established quality standards such as pharmacopoeial monographs are not generally available. The overall aim of the project is to provide pre-qualification and quality assessment of a selected number of pharmaceutical products considered for purchase by UN agencies involved in the procurement of medicines and diagnostics. WHO manages the project and provides technical support and assistance. UNICEF provides administrative support and infrastructure. A spin-off objective is to develop a harmonized quality assessment system for use by public sector procurement agencies.

Progress in pre-qualification has been reported in Volume 16, Number 1 of this journal. The present summary considers experience in pre-qualification of generic HIV medicines and includes the eighth cumulative list of combined innovator and generic products published on 20 August 2003.

Access to generic antiretrovirals

In 2002, the number of people living with HIV/AIDS reached 42 million, with 5 million newly infected cases annually (1). Addressing this crisis demands not only rapid expansion of HIV/AIDS prevention, but also scaling up of treatment and care, including access to HIV/AIDS medicines such as antiretrovirals (ARVs) (2).

Antiretroviral triple-therapy has been effective in industrialized countries in the fight against HIV. However, affordable ARVs are not available in sufficient quantity where they are most needed — Africa, Central and Eastern Europe, and throughout much of Asia and Latin America. Oxfam has recently reported that generic competition can lead to a dramatic drop in prices of AIDS medicines. In Uganda, prices fell by as much as 78% in a few months and by as much as 97% in a 2-year period. The number of patients taking ARVs at one treatment centre increased by 200% within a year (3).

The supply of medicines used in the treatment of HIV/AIDS has become a major concern at both international and country level (5). In addition, recent efforts to accelerate access to HIV-related medicines through negotiation and generic competition have highlighted the importance of ensuring that only quality medicines are procured. Several factors prevent the wider distribution of quality generic ARVs. One of these is the lack of well-established quality specifications and limited experience among generic medicine manufacturers. Efficient procedures therefore need to be in place for compliance and successful pre-qualification of potential suppliers of quality products (2, 5–10).

Pilot procurement, quality and sourcing project for HIV drugs

WHO and UNICEF recognize that the generic pharmaceutical industry has a vital role to play in efforts to provide safe and effective medicines at low cost (4). The purpose of the Pilot Procurement, Quality and Sourcing Project for HIV Drugs (6) is to assess quality, safety and efficacy of products and manufacturing sites. Following assessment of product dossiers and visits to manufacturing facilities by WHO inspectors, pre-

qualified suppliers are confirmed as a reliable supplier and published in a list available on the project website (http://www.who.int/medicines) (6).

Pre-qualification process

Demands for expressions of interest from manufacturers and/or suppliers wishing to take part in the pre-qualification procedure have been regularly published by WHO and other UN agencies. The project objectives have focused on prequalification of the following ARVs (2).

non-nucleoside reverse transcriptase inhibitors: delavirdine, efavirenz, nevirapine
nucleoside reverse transcriptase inhibitors: abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine, lamivudine + zidovudine
protease inhibitors: amprenavir, indinavir, nelfinavir, ritonavir, saquinavir, lopinavir + ritonavir

Specific instructions are provided to manufacturers on how to compile product dossiers and provide relevant data and information on quality, safety and efficacy to comply with WHO standards (6–10). These instructions are available on the project website (6).

Between June 2001 and March 2003, WHO-appointed evaluators have assessed 65 generic ARV product dossiers. The pre-qualification of products, suppliers and manufacturers has been a positive exercise. Of the 65 generic ARV product dossiers submitted for assessment, 14 (21%) were immediately confirmed as meeting WHO recommended international standards (see list on page 160).

For those products and manufacturers not meeting WHO standards, information and advice is provided on how this can be achieved. In many cases, non-compliance occurred because different requirements for registration and licensing of multisource (generic) products (7) are operational within and between countries. For example, bio-equivalence studies may often not be required by some national drug regulatory authorities. Several generic manufacturers have none the less been willing to undertake additional studies (9) including stability testing under WHO recommended conditions as well as bioequivalence studies to ensure compliance of their products with international standards, while manufacturers not meeting WHO good manufacturing practices (GMP) (10) have undertaken to upgrade facilities and implement corrective action.

The latest list of pre-qualified products and manufacturers is set out on pages 158–160 and is also available on the project website (6).

References

1. UNAIDS. *AIDS Epidemic Update 2002*, UNAIDS 02/46E. ISBN 92 9173 253-2 (2002).

2. Scaling Up Antiretroviral Therapy in Resource Limited Settings: Guidelines for a Public Health Approach. http://www.who.int/hiv/pub/prev_care/pub18/en.

3. Oxfam. Generic competition, price and access to medicines —The case of antiretrovirals in Uganda. *Oxfam Briefing Paper No. 26*. http://www.oxfam.org

4. UN Agencies and generic pharmaceutical companies expand access to essential medicines. *FIP News*, Volume 4, No 4, April 2003.

5. *WHO Drug Information*, **16**(1): 31–34 (2002).

6. http://www.who.int/medicines/organization/qsm/activities/pilotproc/pilotprocmain/shtml

7. World Health Organization. WHO Expert Committee on specifications for pharmaceutical preparations. Thirty-fourth report. Annex 9: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. *Technical Report Series*, No. 863, 114–154 (1996).

8. World Health Organization. WHO Expert Committee on specifications for pharmaceutical preparations. Thirty-fourth report. Annex 5. Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. *Technical Report Series*, No. 863, 65–76 (1996).

9. World Health Organization. The use of essential drugs. Annex 3. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. *Technical Report Series,* No. 850, 97–137 (1995).

10. World Health Organization. WHO Expert Committee on specifications for pharmaceutical preparations. Thirty-second report. Good manufacturing practices for pharmaceutical products. Technical *Report Series*, No. 823, 16–22 (1992) GMP

List of pre-qualified products: 20 August 2003

INN	strength	dosage form	supplier	site	packaging
abacavir	300 mg	tablet	GlaxoSmithKline	UK	blister
abacavir	20 mg/ml	oral solution	GlaxoSmithKline	UK	HDPE (bottle)
abacavir	800 mg	dispersable tablet	Cipla	India	blister
abacavir	5%	cream	Cipla	India	Al tube
abacavir	200 mg	tablet	Ranbaxy	India	blister
abacavir	400 mg	tablet	Ranbaxy	India	blister
aciclovir	800 mg	tablet	Ranbaxy	India	blister
amprenavir	15 mg/ml	oral solution	GlaxoSmithKline	UK	HDPE (bottle)
amprenavir	50 mg 150 mg	capsule	GlaxoSmithKline	France	HDPE (bottle)
ceftriazone	500 mg	inj. subst.	Roche	Switzerland	glass vials
ceftriazone	250 mg	Inj. subst.	Roche	Switzerland	glass vials
ciprofloxacin	750 mg	tablet	Lab. Cinfa	Spain	blister
ciprofloxacin	500 mg	tablet	Lab.Cinfa	Spain	blister
ciprofloxacin	250 mg	tablet	Lab.Cinfa	Spain	blister
ciprofloxacin	100 mg	tablet	Cipla	India	blister
ciprofloxacin	250 mg	tablet	Cipla	India	blister
ciprofloxacin	500 mg	tablet	Cipla	India	blister
ciprofloxacin	750 mg	tablet	Cipla	India	blister
ciprofloxacin	250 mg	tablet	Ranbaxy	India	blister (PVC/Al)
ciprofloxacin	500 mg	tablet	Ranbaxy	India	blister (PVC/Al)
ciprofloxacin	750 mg	tablet	Ranbaxy	India	blister (PVC/Al)
clarithromycin	250 mg	tablet	Ranbaxy	India	blister (PVC/PVDC/Al)
clarithromycin	500 mg	tablet	Ranbaxy	India	blister (PVC/PVDC/Al)
cotrimoxazole	200 + 40 mg	syrup	Roche	Switzerland	amber glass bottle
cotrimoxazole	800 +160 mg	tablet	Roche	Switzerland	blister (PVC/Al)
cotrimoxazole	400 + 80 mg	tablet	Roche	Switzerland	blister
didanosine	25 mg	tablet	Bristol Myers Squibb	France	HDPE (bottle)
didanosine	50 mg	tablet	Bristol Myers Squibb	France	HDPE (bottle)
didanosine	100 mg	tablet	Bristol Myers Squibb	France	HDPE (bottle)
didanosine	150 mg	tablet	Bristol Myers Squibb	France	HDPE (bottle)
didanosine	200 mg	chew. or dispersable tablet	Bristol Myers Squibb	France	HDPE (bottle)
fluconazole	50 mg	capsule	Ranbaxy	India	blister
fluconazole	100 mg	capsule	Ranbaxy	India	blister
fluconazole	150 mg	capsule	Ranbaxy	India	blister
fluconazole	200 mg	capsule	Ranbaxy	India	blister
ganciclovir	500 mg	Inj. Subst.	Roche	Switzerland	glass vials
indinavir	400 mg	capsule	Hetero Drugs	India	strip (Al), HDPE bottle
lamivudine	150 mg	tablet	Hetero Drugs	India	strip (Al), HDPE bottle
lamivudine	150 mg	tablet	Ranbaxy	India	blister
lamivudine	150 mg	tablet	Cipla	India	blister
lamivudine	50 mg/5ml	solution	Cipla	India	PET (bottle)
lamivudine	150 mg	tablet	GlaxoSmithKline	UK	HDPE (bottle)
lamivudine	10 mg/ml	oral solution	GlaxoSmithKline	UK	HDPE (bottle)
lamivudine+ zidovudine	150/300 mg	tablet	Ranbaxy	India	blister

INN	strength	dosage form	supplier	site	packaging
lamivudine+ zidovudine	150/300 mg	tablet	Cipla	India	blister
lamivudine+ zidovudine	150 mg + 300 mg	tablet	GlaxoSmithKline	UK	blister HDPE (bottle)
lamivudine+ zidovudine+ abacavir	150 mg+ 300 mg+ 300 mg	tablet	GlaxoSmithKline	UK	blister HDPE (bottle)
nelfinavir mesylate	250 mg	film coated tablet	Roche	Spain, Switzerland	plastic container
nelfinavir mesylate	0.50 mg /ml	oral suspension	Roche	Switzerland	HDPE (bottle)
nevirapine	200 mg	tablet	Ranbaxy	India	blister
nevirapine	200 mg	tablet	Cipla	India	blister
nevirapine	200 mg	tablet	Boehringer Ingelheim	Germany	blister
nevirapine	50 mg /5ml	oral suspension	Boehringer Ingelheim	USA	HDPE (bottle) + syringe
nevirapine	200 mg	tablet	Hetero Drugs	India	strip (Al) HDPE (bottle)
ritonavir	100 mg	capsule	Abbott Laboratories	USA France	HDPE (bottle)
ritonavir	80 mg/ml	oral solution	Abbott Laboratories	UK	PET (bottle)
ritonavir+ lopinavir	33,3 mg + 133,3	capsule	Abbott Laboratories	USA	HDPE (bottle)
ritonavir+ lopinavir	20 mg + 80 mg/ml	oral solution	Abbott Laboratories	UK	PET (bottle)
saquinavir	200 mg	soft capsule	Roche	Germany	glass bottle
saquinavir	200 mg	capsule	Roche	Switzerland	glass bottle
stavudine	15 mg	capsule	Bristol Myers Squibb	France	blister HDPE (bottle)
stavudine	20 mg	capsule	Bristol Myers Squibb	France	blister HDPE (bottle)
stavudine	30 mg	capsule	Bristol Myers Squibb	France	blister HDPE (bottle)
stavudine	40 mg	capsule	Bristol Myers Squibb	France	blister HDPE (bottle)
sulfadiazine	500 mg	tablet	Doms Recordati	France	blister
vinblastine sulfate	10 mg /10 ml	injection	Cipla	India	vial
vincristine sulfate	1mg/ml	injection	Cipla	India	vial
zalcitabine	0.375 mg	tablet	Roche	USA Switzerland	blister (Al) glass bottle
zalcitabine	0.75 mg	tablet	Roche	USA	blister (Al) glass bottle
zidovudine	100 mg	capsule	Combino	Spain	strip (Al)
zidovudine	250 mg	capsule	Combino	Spain	blister PVC/Al
zidovudine	300 mg	capsule	Combino	Spain	blister PVC/Al
zidovudine	300 mg	tablet	Ranbaxy	India	blister
zidovudine	300 mg	tablet	Cipla	India	blister
zidovudine	100 mg	capsule	Cipla	India	HDPE (bottle)
zidovudine	50 mg/5ml	solution	Cipla	India	PET (bottle)

INN	strength	dosage form	supplier	site	packaging
zidovudine	100 mg	capsule	GlaxoSmithKline	UK	blister amber glass bottle
zidovudine	250 mg	capsule	GlaxoSmithKline	UK	blister
zidovudine	10 mg/ml	infusion	GlaxoSmithKline	USA	amber glass vial
zidovudine	50 mg/5 ml	oral solution	GlaxoSmithKline	UK	amber glass bottle
zidovudine	300 mg	tablet	GlaxoSmithKline	UK	blister (PVC/Al) amber glass bottle
zidovudine	300 mg	tablet	Hetero Drugs	India	strip (Al) HDPE bottle

Al: aluminium
HDPE: high density polyethylene
PET: polyethylene terphthalate
PVC: polyvinyl chloride
PVDC: polyvinylidene chloride

**More information on pre-qualification/assessment of manufacturing sites is available on the project website at http://www.who.int/medicines*

List of generic antiretroviral products and manufacturers

INN	strength	dosage form	supplier	country of origin
indinavir	400 mg	capsule	Hetero Drugs	India
lamivudine	150 mg	tablet	Hetero Drugs	India
lamivudine	150 mg	tablet	Ranbaxy	India
lamivudine	150 mg	tablet	Cipla	India
lamivudine	50 mg/5 ml	solution	Cipla	India
lamivudine + zidovudine	150/300 mg	tablet	Ranbaxy	India
lamivudine + zidovudine	150/300 mg	tablet	Cipla	India
nevirapine	200 mg	tablet	Ranbaxy	India
nevirapine	200 mg	tablet	Cipla	India
nevirapine	200 mg	tablet	Hetero Drugs	India
zidovudine	100 mg	capsule	Combino	Spain
zidovudine	250 mg	capsule	Combino	Spain
zidovudine	300 mg	capsule	Combino	Spain
zidovudine	300 mg	tablet	Ranbaxy	India
zidovudine	300 mg	tablet	Cipla	India
zidovudine	100 mg	capsule	Cipla	India
zidovudine	50 mg/5 ml	solution	Cipla	India
zidovudine	300 mg	tablet	Hetero Drugs	India

Consultation Document

The International Pharmacopoeia – monographs for antiretrovirals

Within the framework of the Pilot Procurement Project for Quality and Sourcing of HIV Drugs, the International Pharmacopoeia is collaborating with manufacturers, independent analytical drug quality control laboratories, national and regional pharmacopoeial bodies, research, governmental and regulatory bodies, to provide specifications and monographs for the following antiretroviral agents:

abacavir, didanosine, efavirenz, indinavir, lamivudine, nelfinavir,
nevirapine, ritonavir, saquinavir, stavudine, zidovudine

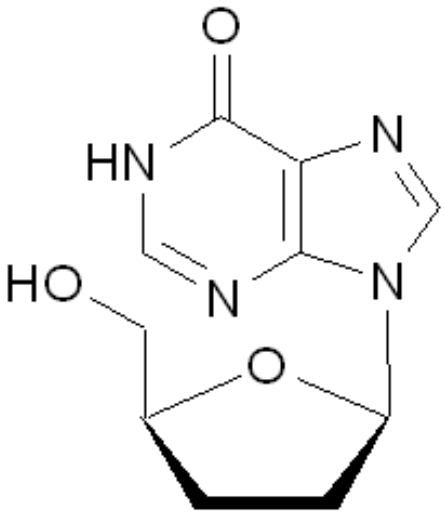
It is planned to develop specifications for the respective dosage forms in a second phase of the project. The first draft monograph, didanosine, is now available for consultation as presented below. Comments are welcome and should be sent to: Quality and Safety: Medicines, World Health Organization, 1211 Geneva 27, Swtizerland or: kopps@who.int

DIDANOSINUM
Didanosine

Molecular formula: $C_{10}H_{12}N_4O_3$

Relative Molecular Mass: 236.23

Graphic formula:



Chemical name: 9-[(2*R*,5*S*)-5-(hydroxymethyl)tetrahydrofuran-2-yl]-1,9-dihydro-6*H*-purin-6-one; 9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-1,9-dihydro-6*H*-purin-6-one; 2',3'-dideoxyinosine (DDI); CAS Reg. No. 69655-05-6.

Description: White to almost-white powder.

Solubility: Sparingly soluble in water; slightly soluble in methanol R and ethanol (~750 g/l) TS.

Category: Antiretroviral (nucleoside reverse transcriptase inhibitor).

Storage: Didanosine should be kept in a well-closed container.

Requirements

General requirement: Didanosine contains not less than 98.5% and not more than 101.0% of $C_{10}H_{12}N_4O_3$, calculated with reference to the dried substance.

Identity test

Carry out the examination as described under "Spectrophotometry in the infrared region" (*International Pharmacopoeia*, Vol. 1, p. 40). The infrared absorption spectrum is concordant with the spectrum obtained from didanosine RS.

If the spectra obtained are not concordant, dissolve the sample in a small amount of methanol R, evaporate and carry out the IR spectrum as mentioned above. Treat didanosine RS in the same way.

Specific Optical Rotation. Use a 10 mg/ml solution and calculate with reference to the dried substance, determined in a 1.0% w/v solution in water; $[\alpha]_D^{20°C}$ = –24.0° to –28.0°.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under "Limit test for heavy metals", Procedure 1 (Vol. 1, p. 118); determine the heavy metal content according to Method A (Vol. 1, p. 119); not more than 20 μg/g.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry for 4 hours at 105 °C; it loses not more than 5 mg/g.

Related Substances. *Note: Prepare fresh solutions and perform the tests without delay*

Carry out the test as described under "High-performance liquid chromatography" (Vol. 5, p. 257), using a stainless steel column (25 cm x 4.6 mm), packed with octadecylsilyl base-deactivated silica gel for chromatography R (5μm). (Hypersil BDS is suitable)

The mobile phases for gradient elution consist of a mixture of aqueous phase (mobile phase A) and methanol (mobile phase B), using the following conditions:

Mobile phase A: A 0.05 M solution of ammonium acetate R adjusted to pH 8.0 using a 20% v/v ammonia solution.

Mobile phase B: methanol.

Time (min)	Mobile phase A (%)	Mobile phase B (%)
	0	90 10
18	90	10
30	75	25
35	75	25
40	90	10
45	90	10

Prepare the following three solutions in a mixture of 90 volumes of mobile phase A and 10 volumes of mobile phase B (dissolution solvent):

For solution (1), dissolve 5 mg of hypoxanthine R and 5 mg of inosine R in the dissolution solvent and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml in 10.0 ml with the same solvent.

For solution (2), dissolve 25 mg of didanosine in the dissolution solvent and dilute to 50.0 ml with the same solvent.

For solution (3), dilute 5.0 ml of solution (2) to 50.0 ml with the dissolution solvent. Then dilute 5.0 ml of this solution to 50.0 ml with the same solvent.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 254 nm.

Inject 20μl of solution (1). The test is not valid unless the resolution factor between the peaks due to hypoxanthine and inosine is greater than 8.0, if necessary reduce the amount of methanol in the mobile phase and adjust the proportion of aqueous phase pH 8.0 accordingly.

Inject separately 20μl of solution (3) in replicate injections in the chromatographic system. The relative standard deviation for peak areas of didanosine in replicate injections of solution (3) is not more than 2.0%.

Inject separately 20μl each of solution (2) and of mobile phase in the chromatographic system. Examine the mobile phase chromatogram for any extraneous peaks and disregard the corresponding peaks observed in the chromatogram obtained with solution (2).

In the chromatogram obtained with solution (2), the peaks are eluted at the following relative retention with reference to didanosine: hypoxanthine = about 0.12; inosine = about 0.26; 2'-deoxyinosine = about 0.33; 2',3'-didehydrodidanosine = about 0.73; didanosine acetate ([(2S,5R)-5-(6-hydroxy-9H-purin-9-yl)-tetrahydro-2-furanyl]methyl acetate) = about 2.86.

Measure the areas of the peak responses obtained in the chromatograms from solutions (2) and (3), and calculate the content of related substances as a percentage. For the calculation of limit contents, multiply the peak areas of the following impurities by the corresponding correction factor: hypoxanthine = 0.65 and 2'-deoxyinosine = 1.4. For any other peaks eluting apart from the above mentioned relative retention, apply a response factor of 1.

In the chromatogram obtained with solution (2) the area of any individual peaks corresponding to hypoxanthine, inosine, 2'-deoxyinosine, 2',3'-didehydrodidanosine and didanosine acetate is not greater than 0.3 times the area of the principal peak obtained with solution (3) (0.3%). Any other impurity peak is not greater than 0.1 times the area of the principal peak obtained with solution (3) (0.1%). The sum of the areas of all peaks, other than the principal peak, is not greater than the area of the principal peak obtained with solution (3) (1.0%). Disregard any peak with an area less than 0.05 times the area of the principal peak obtained with solution (3) (0.05%).

Assay. Dissolve about 0.200 g, accurately weighted, in 50 ml glacial acetic acid R1 and titrate with perchloric acid (0.1 mol/l) VS as described under "Non-aqueous titration"; Method A (Vol. 1, p.131) determining the end point potentiometrically.

Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 23.62 mg of $C_{10}H_{12}N_4O_3$.

Tested impurities

A. "Hypoxanthine" = 1,7-dihydro-6*H*-purin-6-one

B. "Inosine" = 9-β-D-ribofuranosyl-1,9-dihydro-6*H*-purin-6-one

C. "2'-Deoxyinosine" = 9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1,9-dihydro-6*H*-purin-6-one

D. "2',3'-Didehydrodidanosine" = 9-[(2*R*,5S)-5-(hydroxymethyl)-2,5-dihydrofuran-2-yl]-1,9-dihydro-6H-purin-6-one; 9-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)-1,9-dihydro-6*H*-purin-6-one

E. "Didanosine acetate" = 9-[(2*R*,5*S*)-5-[(acetyloxy)methyl]tetrahydrofuran-2-yl]-1,9-dihydro-6*H*-purin-6-one; 9-(5-*O*-acetyl-2,3-dideoxy-β-D-glycero-pentofuranosyl)-1,9-dihydro-6*H*-purin-6-one

Note: Other impurities will also be tested for detection by the methods described.

Reagents

Hypoxantine R. 1,7-dihydro-6*H*-purin-6-one; $C_5H_4N_4O$.

A commercially-available reagent of suitable grade.

Description. A white, crystalline powder.

Solubility. Very slightly soluble in water, sparingly soluble in boiling water, soluble in dilute acids and in dilute alkali hydroxide solutions.

Melting point. Decomposes without melting at about 150 °C.

Thin-Layer Chromatography. Examine as prescribed in the monograph on mercaptopurine (Vol. 4, p.77-79); the chromatogram shows only one principal spot.

Inosine R. 9-β-D-ribofuranosyl-1,9-dihydro-6*H*-purin-6-one; $C_{10}H_{12}N_4O_5$.

A commercially-available reagent of suitable grade.

Description. A white, crystalline powder. Dihydrate, long rectangular plates from water, melting point = 90 °C. Anhydrous needles from 80% alcohol, decomposition 218 °C (rapid heating).

Solubility. Sparingly soluble in water.

Specific optical rotation. $[\alpha]_D^{18°C} = -49.2°$ (c = 0.9 in H_2O with c = concentration by volume, g/100 ml after optical rotation only); $[\alpha]_{white}^{20°C} = -73°$ (0.5 g + 2 ml *N* NaOH +3 ml H_2O).

Silica gel for chromatography, octadecylsilyl, base-deactivated

A very finely divided silica gel, pretreated before the bounding of octadecylsilyl groups by careful washing and hydrolysing most of the superficial siloxane bridges to minimize the interaction with basic components.

Regulatory and Safety Action

Nimesulide temporarily suspended

Finland —The National Agency for medicines, together with the manufacturer, has decided to suspend the distribution, sale and supply of nimesulide (Nimed®) pending a review. Nimesulide is an anti-inflammatory analgesic approved for marketing in January 1998. It is indicated for transient pain, the treatment of pain associated with arthrosis, dysmenorrhoea and fever.

The decision followed reports of severe hepatic adverse reactions. By March 2003, 109 reports had been received by the Agency, 66 of which were of liver effects. Reports involved elevated liver enzymes in cases of hepatitis and isolated cases necessitating liver transplant.

Use of nimesulide is not forbidden, but patients are requested to contact their physician to ensure appropriate use. Any symptoms of liver dysfunction such as malaise, nausea, lack of appetite, abdominal pain or jaundice should be reported immediately.

Reference: Press Release. National Agency for Medicines. http.www.nam.fi, 6 February 2003.

Topiramate: revised prescribing information

United States of America/Canada —The manufacturer of topiramate (Topamax®) has updated the product information based on clinical trial and post-marketing experience in more than 2 million patients worldwide. Rare reports, primarily involving children, have been received of oligohidrosis (decreased sweating) and hyperthermia. Most cases have occurred in association with exposure to elevated environmental temperatures and/or vigorous activity, and children should be observed closely under these conditions. In the majority of patients, topiramate therapy has been continued. Proper hydration before and during activities such as exercise or exposure to warm temperatures is recommended.

As of February 2002, the rate for spontaneous postmarketing reports of all potential cases of oligohidrosis is approximately 35 per 1 000 000 patients treated and 1.6 per 1 000 000 patients treated for serious or medically significant oligohidrosis or its sequelae. It is generally recognized that postmarketing data are subject to substantial under-reporting.

Caution should be used when topiramate is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.

Patients, especially paediatric patients, should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather.

References

1. Undated letter from Ortho-McNeil Pharmaceutical. http://www.fda.gov/medwatch.

2. Letter from Janssen-Ortho dated 11 July 2003. http://www.hc-sc.gc.ca

Omalizumab for allergy-related asthma

United States of America —The Food and Drug Administration (FDA) has approved the first biotechnology product to treat patients with allergy-related asthma. Omalizumab (Xolair®), is a monoclonal antibody shown to be safe and effective for patients with moderate to severe allergy-related asthma inadequately controlled with inhaled corticosteroid treatments. In these patients, omalizumab has been shown to decrease the number of asthma exacerbations or episodes of airway narrowing that result in wheezing, breathlessness, and cough. The product is given as an injection under the skin.

As a second-line treatment, it is recommended when first-line treatments have failed; it is not approved for children under the age of 12 and is only for patients with moderate to severe, allergy-

related asthma. Only patients who have asthma caused by allergies — to be established by skin or blood test before treatment — can benefit from this new treatment.

The effectiveness of omalizumab was mainly assessed in two placebo-controlled studies of over 1000 adolescents and adults lasting six months. These patients all had persistent symptoms despite the use of inhaled corticosteroids. About 80–85% of patients treated with omalizumab had no exacerbation of their asthma symptoms compared to about 70–75% of placebo treated patients. During clinical trials, more patients treated with omalizumab developed a new or recurrent cancer (0.5%) compared to control patients (0.2%). The sponsor is planning long-term studies in an attempt to determine whether there is a relationship.

The other major safety concern was severe allergic reactions or anaphylaxis. Anaphylaxis occurred in three patients who all responded and recovered following medical treatment.

Reference: *FDA Talk Paper*, T03-49, 20 June 2003.

Co-packaged treatments for cerebrovascular events

United States of America — The Food and Drug Administration (FDA) has approved Pravigard PAC® (co-packaged pravastatin sodium and buffered aspirin tablets) for use when treatment is appropriate. Pravachol and buffered aspirin are indicated for reducing the occurrence of cardiovascular events, including death, myocardial infarction or stroke in patients with clinical evidence of cardiovascular and/or cerebrovascular disease. Patients should also be placed on a standard cholesterol-lowering diet.

Pravigard PAC® should not be taken by patients who have certain liver or kidney problems, women who are pregnant or planning to become pregnant, individuals less than 18 years of age or by individuals who are allergic to nonsteroidal anti-inflammatory (NSAID) medicines or any of the ingredients in Pravigard PAC®.

Possible serious side effects include muscle or liver damage, bleeding and stomach problems. Patients should report unexplained muscle pain or weakness, unusual bleeding, heartburn, nausea or vomiting, stomach pain or bowel movements or stools that look like black tar. Liver function tests may be performed prior to initiation of treatment.

Reference: *FDA Talk Paper*, T03-51, 25 June 2003

OTC omeprazole approved for heartburn

United States of America — The Food and Drug Administration (FDA) has approved omeprazole (Prilosec OTC®), the first over-the-counter treatment for frequent heartburn.

Unlike the two classes of currently marketed over-the-counter heartburn treatments, antacids and acid reducers, omeprazole is indicated for the treatment of heartburn that occurs two or more days per week (frequent heartburn). It stops acid production at its source. Omeprazole is currently widely prescribed for frequent heartburn and other related but more serious problems that need the care of a physician. Omeprazole is not for people who have heartburn infrequently — one episode of heartburn a week or less — or for those who want immediate relief of heartburn.

Although side effects from omeprazole are not common they can include: headache, diarrhoea, constipation, upset stomach, vomiting, stomach pain, cough, cold symptoms, dizziness and rash.

Prescription-only omeprazole, first approved by FDA in 1989, will remain available for diseases that require diagnosis and supervision by a doctor, such as gastro-oesophageal reflux disease (GERD), inflammation of the oesophagus (oesophagitis) and ulcers.

Because of the safety studies being performed by the manufacturer, this product will have three years of over-the-counter exclusivity. Generic versions of the prescription product will not be able to market an OTC version until the marketing exclusivity has expired.

Reference: *FDA News*, P03-48. 20 June 2003.

Recombinant antihaemophilic factor licensed

United States of America — The Food and Drug Administration (FDA) has licensed a new recombinant DNA-derived clotting factor to treat

people with haemophilia A. This new anti-haemophilic human factor VIII product is the first produced without using additives derived from human or animal blood in the manufacturing process.

The new product, ADVATE® Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method (rAHF-PFM), is approved to prevent and control bleeding episodes or to prepare persons with haemophilia for surgery. It is produced by genetically engineered Chinese hamster ovary cells that have been altered to produce factor VIII.

Current factor VIII products (both plasma-derived and recombinant) are considered very safe as a result of many technological advances in the last two decades. These include viral inactivation and removal steps in manufacturing that are believed to effectively prevent transmission of hepatitis B, hepatitis C or HIV from plasma-derived products. These same procedures are considered effective to minimize any infectious risks from products made by DNA technology, which uses living cells. None of these products is reported to have transmitted HIV, hepatitis B or hepatitis C since 1987.

The first recombinant antihaemophilic factor was approved in 1992. However, until now, all recombinant factor VIII products were made with blood-derived additives of human or animal origin, such as albumin. These additives were needed to keep the cells viable so they could make the factor VIII protein.

Reference: *FDA Talk Paper*, T03-55. 25 July 2003

New diabetes device approved

United States of America — The Food and Drug Administration (FDA) has cleared the first device for diabetics which integrates a glucose meter and insulin pump with a dose calculator. The new device could be the first step in the development of a fully automated glucose monitoring and insulin delivery system.

The product, made by Medtronic MiniMed, Inc., and Becton Dickinson, combines the Medtronic MiniMed Paradigm insulin pump® with a Becton Dickinson glucose monitor and facilitates data interchange between the two. It has additional circuitry and software modifications that allow it to transmit glucose values to the insulin pump and to transfer data between the insulin pump and a personal computer running the appropriate Medtronic MiniMed® communications software. Since the glucose meter calculates and transmits information to the insulin pump automatically, it prevents the errors that can sometimes result when patients input this data manually. In addition, use of the integrated system is expected to make it more convenient for people to manage their diabetes.

FDA cleared the device for marketing based on safety and effectiveness of the separately marketed components and on reviews of the new device configuration, software, usability studies and electromagnetic interference compatibility testing conducted by the firms.

Reference: *FDA Talk Paper,* P03-49. 7 July 2003.

Recombinant somatropin approved for short stature

United States of America — The Food and Drug Administration (FDA) has approved a new indication for somatropin, rDNA origin, for injection (Humatrope®), a brand of growth hormone, for the long-term treatment of children with idiopathic short stature, also called non-growth hormone deficient short stature.

“Short stature” has been defined by the American Association of Clinical Endocrinologists and the Growth Hormone Research Society as height more than 2 standard deviations (SD) below the mean for age and sex. This corresponds to the shortest 2.3 percent of children. This new indication restricts therapy to children who are even shorter, specifically more than 2.25 SD below the mean for age and sex, or the shortest 1.2% of children.

Approval was based on two randomized, multicentre trials, conducted in approximately 300 children with idiopathic short stature after excluding other causes, including growth hormone deficiency.

The pivotal trial was a randomized, double-blind study in 71 children aged 9–15 years. Patients received injections of either Humatrope® or placebo three times weekly until adult height was reached. Thirty-three patients contributed final height measurements after a mean treatment duration of 4.4 years. Mean final height of patients exceeded that of the placebo patients by approximately 1.5 inches.

In a second study, patients received one of three increasing doses in divided doses six times weekly. The average duration of treatment to final height was 6.5 years. Final height exceeded that predicted at the time of enrolment in the majority of patients, and by up to nearly four inches in some. In the high-dose group, mean final height exceeded mean height predicted at baseline by nearly three inches.

The safety profile in children with idiopathic short stature did not differ from that in children with other conditions for which growth hormone is indicated.

Various growth hormone products are currently indicated in children for short stature associated with growth hormone deficiency, chronic renal insufficiency, Turner syndrome, Prader-Willi syndrome, and in children born small for gestational age.

The manufacturer has advised FDA that it will not engage in direct-to-consumer advertising and will limit the marketing of this product for this new use to paediatric endocrinologists only to better ensure proper use in the indicated population. In addition, the manufacturer intends to tightly control distribution.

Reference: http://www.fda.gov/medwatch 30 May 2003.

Diagnostic test for West Nile virus

United States of America — The Food and Drug Administration (FDA) has approved the first test for use in the clinical laboratory diagnosis of West Nile virus infection. West Nile Virus IgM Capture ELISA® is intended for use in patients with clinical symptoms consistent with viral encephalitis/ meningitis.

The new test works by detecting the levels of a particular type of antibody, IgM, to the disease in serum. IgM antibodies can be detected within the first few days of the onset of illness and can assist in the diagnosis of these patients.

The assay was evaluated using over 1000 patient sera tested at four different clinical sites. The test correctly identified antibody in 90–99% of cases. Because detection of antibody is not always specific in patients with acute viral infections, this test is considered presumptive and should be confirmed by more specific testing. Although the test is a valuable aid in the diagnosis of West Nile virus encephalitis, due to similarities with other viruses in the same family, there is a need to confirm positive results by an additional test or by using the current CDC diagnostic guidelines.

West Nile virus is a mosquito-borne virus which first appeared in the United States in 1999. While the virus often presents as a mild infection that clears without further treatment, some patients develop severe infection resulting in neurological disease and even death. The disease is most prevalent during the peak mosquito season. Over the past several years, the geographic range of the virus as well as the number of new infections has expanded and now covers most of continental United States.

Reference: *FDA Talk Paper,* P03-51. 9 July 2003.

Etanercept for ankylosing spondylitis

United States of America — The Food and Drug Administration (FDA) has approved an application for etanercept (Enbrel®), a genetically-engineered protein, for a new indication for treatment of patients with active ankylosing spondylitis (AS), a chronic inflammatory disease affecting primarily the lower back and joints. Etanercept is also licensed for treatment of patients with rheumatoid arthritis, juvenile rheumatoid arthritis, and psoriatic arthritis.

The disease affects men more often than women. Symptoms of the disease may start in adolescence and are usually present by age 30. Patients often have lower back pain and stiffness, chest pain, joint pain and swelling, and tenderness due to inflammation. In some patients the disease can cause significant pain and disability for many years.

Etanercept binds to tumour necrosis factor (TNF), a naturally occurring protein in the body, and inhibits its action. TNF, promotes inflammation in the body and is found at elevated levels in the blood and certain tissues of patients with AS. It is believed that interference with TNF plays a role in the beneficial effects of etanercept for AS.

The major efficacy trial of etanercept for AS was a randomized, double-blind, placebo-controlled study of 277 patients. The study excluded patients with the most severe forms of AS. After six months of twice-weekly treatments, 58% of

patients who received etanercept showed significant improvement on a scale that measured pain, function, and inflammation compared to 23% who received a placebo.

In the study , the main side effects of etanercept were similar to those previously seen for this drug for other indications, including injection site reactions and upper respiratory infections. The approved labelling warns physicians about post-marketing reports of serious infections. Etanercept should not be given to patients with any active infection, including chronic or localized infections. It also recommends that patients who develop a new infection should be monitored closely.

Reference: *FDA Talk paper*, T03-54 24 July 2003

Porfimer sodium approved for Barrett oesophagus

United States of America — The Food and Drug Administration (FDA) has approved porfimer sodium Injection (Photofrin®) for the ablation of precancerous lesions (high-grade dysplasia) in Barrett oesophagus patients who do not undergo surgery to remove the oesophagus (oesophagectomy).

Barrett oesophagus is a condition in which oesophagus lining is replaced by a type of tissue similar to that normally found in the intestine. Barrett oesophagus is estimated to affect about 700 000 adults in the United States. It is associated with the very common condition gastro-oesophageal reflux disease or GERD.

While Barrett oesophagus may cause no symptoms itself, a small number of people with this condition develop pre-cancerous lesions that progress to an often deadly type of cancer of the oesophagus called oesophageal adenocarcinoma.
Porfimer sodium is a photosensitizing agent used in photodynamic therapy (PDT), a treatment for some types of cancer. PDT is based on the discovery that photosensitizing agents can kill one-celled organisms when the organisms are exposed to a particular type of light. PDT destroys cancer cells through the use of a laser light in combination with a photosensitizing agent. FDA first approved porfimer sodium in 1998.

The clinical study supporting this new use of Photofrin PDT® showed that patients were more likely to achieve complete reversal of their pre-cancerous lesions in Barrett oesophagus and had an 80% chance of being cancer-free. However, the effectiveness of Photofrin PDT® in reducing the long-term risk of oesophageal cancer has not been demonstrated.

Side effects include photosensitivity reactions and oesophageal strictures. Precautions should be taken to avoid exposure of skin and eyes to bright light.

Reference: *FDA Talk paper,* T03-60 4 August 2003

New drug approved for lowering cholesterol

United States of America — The Food and Drug Administration (FDA) has approved a new HMG-CoA reductase inhibitor, rosuvastatin (Crestor®), to lower cholesterol.

Rosuvastatin was approved based on multiple trials of at least 6 weeks' duration in which rosuvastatin treatment was compared to placebo and other marketed statins. In these trials, rosuvastatin reduced total-C, LDL-C, and TG and increased HDL-C with therapeutic response occurring within one week and maximum response seen at four weeks. Approximately 12 000 patients received rosuvastatin at different doses.

The most frequent side effects seen in patients treated with rosuvastatin included muscle aches, stomach pain, constipation, nausea, and weakness. In rare instances, severe muscle pain and muscle weakness resulting in kidney damage have been associated with statin drugs. If general muscle aches persist, patients should call their physician. Patients should be monitored for abnormalities of liver function before treatment, at 12 weeks following initial therapy and with any elevation of dose. Monitoring is recommended periodically thereafter.

Reference: *FDA Talk paper*, T03-6, 12 August 2003

Regulatory Challenges

Regulation of fixed-dose combination products

Internationally, there is an increasing trend to license fixed-dose combination products for the market. In less well-resourced countries, fixed-dose combination products (FDCs) hold a particular attraction in the treatment of communicable diseases such as tuberculosis, malaria and HIV because of both their lower cost and the reduced complexity of procurement and distribution. However, for a drug regulatory authority, a number of specific questions need to be addressed before applications to register FDCs can be licensed. Such issues include whether the combination is rational, or whether it will encourage inappropriate prescribing.

What is a fixed-dose combination?

The term fixed-dose combination product is synonymous with fixed-ratio combination product. Both terms refer to a product that contains two or more active ingredients. Because the product is of a defined composition, the two (or more) ingredients are present in a fixed ratio. Hence the term "fixed dose" or "fixed ratio" combination.

Such a product may be available in more than one strength, each of which may itself be a fixed dose combination and may contain different ratios of active ingredients. For example, Augmentin Duo Forte® tablets contain 850 mg of amoxicillin and 125 mg of clavulanic acid (a ratio of 6.8□:□1) whereas Augmentin Forte® tablets contain 500 mg of amoxicillin and 125 mg of clavulanic acid (a ratio of 4.0□:□1). Different ratios can be rational in particular circumstances.

Advantages of fixed-dose combinations

The presumed advantages of FDCs include:

- Drugs that are normally given in combination are more conveniently prescribed and consumed as an FDC.
- Better patient compliance is claimed (but see below).
- It is cheaper to purchase an FDC product than to purchase the products separately.
- The logistics of procurement and distribution are simpler (which can be especially important in remote areas).

Disadvantages of fixed-dose combinations

Critics of FDCs suggest that:

- FDCs discourage separate titration of each active ingredient. This is a particular problem when both of the active ingredients require dose titration. Indeed, it can be argued that the very existence of an FDC discourages adjustment of doses to the patient's needs (if that is appropriate for the combination in question).
- When the active ingredients in question have different pharmacokinetics and/or pharmacodynamics, an FDC may not be appropriate.
- Unless both of the active ingredients are available as separate entities, FDCs encourage polypharmacy irrespective of whether it is appropriate for a particular patient.

Patient compliance

There is a general assumption that FDCs will achieve better patient compliance than prescription of the same actives in separate products. This belief would appear to be intuitive rather than evidence-based. A recent Cochrane review (1) examined available evidence as to the value of interventions in improving patient adherence to medication schedules. In terms of dose schedules, the major factor affecting patient compliance appears to be the number of occasions on which a patient takes medication in a day, with adherence to regime decreasing for three or more dosing events per day. The effect on compliance of using FDCs rather than two or more single entity products appears not to have been studied (2).

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Cost and logistics

Minimizing costs and simplifying the logistics of procurement and distribution of complex antimicrobial regimes are legitimate objectives in achieving public health outcomes in less well-resourced nations. FDCs can usefully contribute to both of these elements, but only if they do not compromize therapeutic outcomes.

Considerations for drug regulation

WHO has made the following comments about FDCs. "New fixed-ratio combination products are regarded as new drugs in their own right. They are acceptable only when (a) the dosage of each ingredient meets the requirements of a defined population group, and (b) the combination has a proven advantage over single compounds administered separately in terms of therapeutic effect, safety or compliance. They should not be treated as generic versions of single-component products" (3, 4).

A busy prescriber may be tempted to select an FDC when patient titration of the individual active ingredients would be the better course. Combinations of anti-hypertensives might be an example. The busy prescriber may not have read the prescribing information for the FDC to enable him/her to determine the circumstances in which it is appropriate therapy, and the circumstances in which separate titration of the active ingredients would be in the patient's interest. This is an example of what might be described as inappropriate prescribing.

Similarly, prescribing of an opiate in combination with paracetamol only because it is an available FDC could be described as inappropriate. If the patient needs high-dose analgesic therapy, this combination might contribute to hepatotoxicity via the parecetamol component. However, there certainly may be circumstances in which the FDC is an appropriate combination. A number of regulatory authorities have published guidelines that attempt to establish the principles that define those circumstances. The following table lists regulatory guidelines on the subject of fixed-dose combination products.

References

1. Haynes, R.B., McDonald, H., Garg, A.X. Interventions for helping patients to follow prescriptions for medications. *Cochrane Library*, Update Software, Issue 2. Oxford, England. 2002.

2. Haynes, R.B. Personal communication, 2003.

3. World Health Organization. The Use of Essential Drugs. Seventh report of the WHO Expert Committee. *Technical Report Series*, No. 867 (1997).

4. World Health Organization. *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: A manual for a Drug Regulatory Authority*. WHO/DMP/RGS/98.5 (1998).

Guidelines on fixed-dose combination products

Title, publisher & date	Notes
United States of America	
Fixed-combination prescription drugs for humans. Food and Drug Administration. FDA 21CFR300.50 (Revised 1 April 2003). Federal Register, on: http://www.accessdata.fda.gov/scripts/cdrh/cfd	Approx 250 words. In terms of safety and efficacy, describes the circumstances in which active ingredients may be combined in an FDC.
Conjugated estrogens, USP-LC-MS method for both qualitative chemical characterization and documentation of qualitative pharmaceutical equivalence. FDA June 2000 (draft). http://www.fda.gov/cder/guidance/3668dft.pdf	Seven pages. This guideline relates only to conjugated estrogens from a biological source, normally pregnant mares' urine, which contains multiple estrogens. There have been difficulties in preparing generic equivalents of this type of product. The guideline specifies how chemical equivalence can be demonstrated.

Title, publisher & date	Notes
Estrogen & Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation. FDA January 2003 (draft). http://www.fda.gov/cder/guidance/5412dft.pdf	Ten pages. This guideline is not restricted to estrogens from a biological source. Approval will be based on two criteria: • That each component contributes to safety and efficacy as defined in 21CFR300.50, and • The FDC contains the lowest effective dose of each of the active ingredients for their respective labelled indication.
National Uniformity for Nonprescription Drugs — Ingredient Listing for OTC Drugs FDA, April 1998 — Procedural guidance. http://www.fda.gov/cder/guidance/2219fnl.pdf	Two pages. Cross-refers to proposed and existing legislation. Defines a standardized format of labelling of active and inactive ingredients, including nomenclature, doses and order of listing of ingredients.
Enforcement Policy on Marketing OTC Combination Products. FDA, March 1998 http://www.fda.gov/cder/guidance/old001fn.pdf	Three pages. Describes possible action by sponsors following a recommendation as to regulatory action after review of a category of OTC product and, possibly, establishment of a monograph.
(a)(4)(iv) in: Procedures for Classifying OTC Drugs as Generally Recognized as Safe and Effective and not Misbranded, and for Establishing Monographs. FDA 21CFR330.10 in Federal Register, January 2002 http://www.accessdata.fda.gov/scripts/cdrh/cfd	Approx 80 words. In terms of safety and efficacy, describes the circumstances in which active ingredients may be combined in an OTC product. Specifies there must be adequate directions for use and warnings against unsafe use.
General Guidelines on OTC Combination Products. In Federal Register, March 1998. http://www.fda.gov/cder/guidance/old002fn.pdf	Two pages. Cross-refers to (a)(4)(iv) in FDA 21CFR330.10 (see above) and further defines the circumstances (safety and efficacy) in which two or more active ingredients may be com bined in an OTC product. Specifies that OTC monographs will list permitted combinations (in the context of GRAS reviews of OTC products and establishment of monographs.
Australia	
Fixed-combination products in: Australian Guidelines for the Registration of Drugs. Vol. 1. Therapeutic Goods Administration (TGA) 1994. http://www.health.gov.au/tga/docs/html/agrd1.htm	Approx 250 words. Discusses justification of the combination in terms of either pharmacodynamics or demonstrated therapeutic effect.
International Conference on Harmonization (ICH)/ Europe	
Fixed combination products in ICH principles document for clinical evaluation of new antiihypertensive drugs. Part 6 (Draft). ICH/CPMP/541/00 (draft). http://www.ich.org/pdfICH/e12.pdf	Approx 250 words. Describes two experimental designs for safety and efficacy studies on FDCs of antihypertensives, namely factorial studies and studies in patients who have failed to respond adequately to each of the drugs given separately.

Title, publisher & date	Notes
Fixed combinations in Note for guidance on Clinical Investigation of Medicinal Products in the Treatment of Hypertension. Part 7. CPMP Nov 1997 – CPMP/EWP/238/96 Rev1 http://www.emea.eu.int/pdfs/human/ewp/023895en.pdf	Three pages that: • describe the circumstances (in terms of safety and efficacy) in which FDCs may be acceptable in the therapy of hypertension, and • provide advice on their clinical development as first or second-line therapy. NB: The section on FDCs in this guideline is different to the draft ICH guideline on new antihypertensives.
Fixed-Combination Medicinal Products. CPMP April 1996 — CPMP/EWP/240/95, III/5773/94 (formerly known as: Testing and Licensing Criteria for Fixed Combination Medicinal Products). http://www.emea.eu.int/pdfs/human/ewp/024095en.pdf	Four pages that: • require justification of the particular combination • give examples of circumstances (safety and efficacy) in which FDCs may be acceptable • describe principles that define acceptable indications • require consideration of possible pharmacokinetic and pharmacodynamic interactions • require evidence as to safety and efficacy (allowing bibliographic data as supportive evidence in certain circumstances) • require evidence on safety and efficacy of the doses selected. Also applicable to a new chemical substance which dissociates in vivo into two well known active substances. Substances having a critical dosage range or a narrow therapeutic index are unlikely to be suitable for inclusion in fixed combinations.
Fixed combination products in: Note for Guidance on the Investigation of Bioavailability & Bioequivalence. 5.1.5 CPMP July 2001. CPMP/EWP/QWP/1401/98http://www.emea.pdfs/eu.int/human/ewp/140198en.pdf	Approx 50 words. States that FDCs should in general be assessed as to the bioavailability and bioequivalence of the individual active ingredients either separately (in the case of a new combination) or as an existing combination. Studies should be designed to detect any pharmacokinetic drug-drug interaction.
Note for Guidance on Fixed Combinations of Herbal Medicinal Products with Long-Term Marketing Experience. Guidance to Facilitate Mutual Recognition and Use of Bibliographic Data. CPMP, January 1999. EMEA/HMPWP/15/99. http://www.emea.eu.int/pdfs/human/hmpwp/001599en.pdf	Three pages. Very similar content to Fixed-Combination Medicinal Products, CPMP, April 1996. CPMP/EWP/240/95, III/5773/94 (above). Requirements in relation to safety aspects and therapeutic data cross-refer to other guidelines on herbal medicinal products. Possible pharmacokinetic and pharmacodynamic interactions must be discussed as far as data are available.
The ratio and/or fixed content of one component of a combination drug product (IV.3). In: Points to Consider on Pharmacokinetics and Pharmacodynamics in the Development of Antibacterial Medicinal Products. CPMP, July 2000. CPMP/EWP/2655/99 http://www.emea.eu.int/pdfs/human/ewp/265599en.pdf	Seven pages. This guideline discusses the relationship between plasma concentration/time profiles and clinical efficacy. Selection of a suitable ratio of doses for FDCs is discussed in Part IV.3 (approx 100 words).

ATC/DDD Classification (final)

The following final anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 23–24 October 2002. They came into force on 1 March 2003 and are included in the January 2004 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, e-mail: whocc@nmd.no.

ATC level	INN/Common name	ATC code
New ATC level codes (other than 5th level):		
Direct thrombin inhibitors		B01AE
Other anterior pituitary hormones and analogues		H01AX
Prostaglandin analogues		S01EE
New ATC 5th level codes:		
	adalimumab	L04AA17
	adefovir dipivoxil	J05AF08
	afelimomab	L04AA16
	alefacept	L04AA15
	aluminium diacetate	D10AX05
	argatroban	B01AE03
	benidipine	C08CA15
	beraprost	B01AC19
	bimatoprost	S01EE03
	carbon dioxide	V03AN02
	ciclesonide	R03BA08
	combinations	D06AX30
	docosanol	D06BB11
	eflornithine	D11AX16
	eprosartan and diuretics	C09DA02
	ertapenem	J01DH03
	etilevodopa and decarboxylase inhibitor	N04BA06
	etoricoxib	M01AH05
	everolimus	L04AA18
	fasudil	C04AX32
	frovatriptan	N02CC07
	glutaral	D08AX09
	gusperimus	L04AA19
	helium	V03AN03
	insulin aspart	A10AD05
	lanthanum carbonate	V03AE03
	levodopa, decarboxylase inhibitor and COMT inhibitor	N04BA03
	levofloxacin	S01AX19
	lofexidine	N07BC04

ATC level	INN/Common name	ATC code
	lovastatin, combinations	C10AA52
	melagatran	B01AE04
	melevodopa	N04BA04
	melevodopa and decarboxylase inhibitor	N04BA05
	methotrexate	L04AX03
	moxonidine and diuretics	C02LC05
	nitrogen	V03AN04
	oxygen	V03AN01
	pegvisomant	H01AX01
	pimecrolimus	D11AX15
	polygeline	B05AA10
	rifampicin, pyrazinamide and isoniazid	J04AM05
	rifampicin, pyrazinamide, ethambutol and isoniazid	J04AM06
	rifapentin	J04AB05
	telmisartan and diuretics	C09DA07
	travoprost	S01EE04

ATC codes changes:

Previous:	desirudin	B01AX02
New:	desirudin	B01AE01
Previous:	latanoprost	S01EX03
New:	latanoprost	S01EE01
Previous:	lepirudin	B01AX03
New:	lepirudin	B01AE02
Previous:	unoprostone	S01EX04
New:	unoprostone	S01EE02

ATC name changes:

Previous:	ethambutol, combinations	
New:	ethambutol and isoniazid	J04AM03
Previous:	rifampicin, combinations	
New:	rifampicin and isoniazid	J04AM02
Previous:	somatropin and analogues	
New:	somatropin and somatropin agonists	H01AC
Previous:	streptomycin, combinations	
New:	streptomycin and isoniazid	J04AM01
Previous:	thioacetazone, combinations	
New:	thioacetazone and isoniazid	J04AM04

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
anakinra	0.1	g	P	L04AA14
bosentan	0.25	g	O	C02KX01
dutasteride	0.5	mg	O	G04CB02
ertapenem	1	g	P	J01DH03
etoricoxib	60	mg	O	M01AH05
fentanyl	0.6	mg	SL	N02AB03
ferric oxide dextran complex	0.1	g Fe^{3+}	P	B03AC06

INN/common name	DDD	Unit	Adm.R	ATC code
fondaparinux	2.5	mg	P	B01AX05
frovatriptan	2.5	mg	O	N02CC07
fulvestrant	8.3	mg	P	L02BA03
gatifloxacin	0.4	g	O, P	J01MA16
glatiramer acetate	20	mg	P	L03AX13
lofexidine	1.4	mg	O	N07BC04
memantine	20	mg	O	N06DX01
miglustat	0.3	g	O	A16AX06
mometasone	0.4	mg	Inhal.powder	R03BA07
octreotide	0.7	mg	P	H01CB02
peginterferon alfa-2a	26	mcg	P	L03AB11
risperidone	1.8	mg	P depot	N05AX08
tenecteplase	40	mg	P	B01AD11
tenofovir disoproxil	0.245	g	O	J05AF07
tiotropium bromide	18	mcg	Inhal.powder	R03BB04
voriconazole	0.4	g	O, P	J02AC03
ziprasidone	40	mg	P	N05AE04

Change of DDDs:

INN/common name	Previous DDD	Unit	Adm.R	New DDD	Unit	Adm.R	ATC code
levofloxacin	0.25	g	O, P	0.5	g	O, P	J01MA12

ATC/DDD Classification (temporary)

The following temporary anatomical therapeutic chemical (ATC) classifications, defined daily doses (DDDs) and alterations were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 26 – 27 May 2003. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, e-mail: whocc@nmd.no.before 15 September 2003. If no objections are received before this date, the new ATC codes and DDDs will be considered final and be included in the January 2004 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

ATC level	INN/Common name	ATC code
New ATC 5th level codes:		
	atomoxetine	N06BA09
	bemiparin	B01AB12
	bortezomib	L01XX32
	celecoxib	L01XX33
	combinations	B02BC30
	dextriferron	B03AD04
	drospirenone and estrogen	G03FA17
	efalizumab	L04AA21
	emtricitabine	J05AF09
	epinastine	S01GX10
	gemtuzumab	L01XC05
	levosulpiride	N05AL07
	lumiracoxib	M01AH06
	metformin and rosiglitazone	A10BD03
	minocycline	A01AB23
	nesiritide	C01DX19
	norelgestromin and estrogen	G03AA13
	solifenacin	G04BD08
	sulfadiazine and tetroxoprim	J01EE06
	triclabendazole	P02BX04
	trimegestone and estrogen	G03FA16
ATC code changes		
Previous:	budesonide	H02AB16
New:	budesonide	A07EA06
Previous:	trospium	A03AB20
New:	trospium	G04BD09

ATC name changes:

	ATC level	ATC code
Previous:	Biguanides and sulfonamides in combination	
New:	Combinations of oral blood glucose lowering drugs	A10BD
Previous:	Corticosteroids for local use	
New:	Corticosteroids acting locally	A07EA
Previous:	Psychostimulants and nootropics	
New:	Psychostimulants, agents used for ADHD and nootropics	N06B

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
adefovir dipivoxil	10	mg	O	J05AF08
alprostadil	0.5	mg	P	C01EA01
bemiparin	2.5	TU	P	B01AB12*
clarithromycin	1	g	P	J01FA09
disulfiram	0.2	g	O	N07BB01
drotrecogin alfa (activated)	40	mg	P	B01AD10
eptifibatide	0.2	g	P	B01AC16
ezetimibe	10	mg	O	C10AX09
imiglucerase	300	U	P	A16AB02
minocycline	1	mg	O	A01AB23*
oseltamivir	0.15	g	O	J05AH02
parecoxib	40	mg	P	M01AH04
pegfilgrastim	0.3	mg	P	L03AA13
pegvisomant	10	mg	P	H01AX01
procaine penicillin	0.6	g	P	J01CE09
rosuvastatin	10	mg	O	C10AA07
tadalafil	10	mg	O	G04BE08
teriparatide	20	mcg	P	H05AA02
valdecoxib	10	mg	O	M01AH03
vardenafil	10	mg	O	G04BE09

* Temporary ATC code

Change of DDDs

INN/common name	Previous DDD	Unit	Adm.R	New DDD	Unit	Adm.R	ATC code
bezitramide	10	mg	O	15	mg	O	N02AC05
galantamine	24	mg	O	16	mg	O	N06DA04
hydromorphone	4	mg	O	20	mg	O	N02AA03
leflunomide	15	mg	O	20	mg	O	L04AA13
oxycodone	30	mg	O	75	mg	O	N02AA05
repaglinide	6	mg	O	4	mg	O	A10BX02
rofecoxib	12.5	mg	O	25	mg	O	M01AH02