

WHO Drug Information

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Drug Management

Cost containment and generic substitution

Expenditure on medicines accounts for a major proportion of public health costs and governments increasingly focus on ways to reduce the burden on public spending. Overall, generic drugs are substantially less expensive than branded products and their promotion can lead to a reduction in drug costs and increased availability. Generic substitution is a cost-effective strategy for containing drug expenditure and has considerable potential for contributing to cost savings. The aim of generic substitution is to provide an economic incentive for countries with health insurance schemes to promote the use of low/cost generic equivalents. Recent experience in Finland shows how substitution with a cheaper alternative increased competition between pharmaceutical companies and led to substantial cost savings amounting to nearly 40 million in six months. The amount saved in one year was approximately 5% of the total cost of all reimbursed medicines.

Generic substitution in Finland

Generic substitution aims at promoting cost-effective medical treatment. Savings are made both by actually replacing products with less expensive alternatives, and by promoting tougher price competition between pharmaceutical companies. Beginning in April 2003, more than 700 000 patients in Finland have since found that one or more of the refundable drugs they have been receiving have been replaced with a less expensive generic counterpart.

The drugs most frequently replaced included antihistamines, antidepressants and lipid-reducing agents. Two-thirds of the cost savings have been generated by reductions in the price of medicinal products considered appropriate for substitution. The savings generated by generic substitution have offset, in particular, the increase in drug costs generated by growing use of new, more costly drugs.

Generic substitution was introduced in Finland in April 2003. This new practice required the pharmacies to replace the medicinal product prescribed by a doctor with a less expensive generic counterpart unless the doctor forbids or the buyer declines the replacement. The National Agency for Medicines decides which generic counterpart can be substituted for another drug, and maintains a list of approved substitutable medicines.

Generic substitution operates within a price “corridor”. Prescribed products are replaced with the cheapest or close to the cheapest interchangeable generic or parallel import product. The lowest limit within this corridor is the lowest price of a substitutable product and the upper limit, achieved by adding 2 to the lowest price, if the least expensive product costs less than 40; or 3, if the least expensive product costs 40 or more. The price corridor for different groups of substitutable drugs is established quarterly following price notifications submitted by pharmaceutical companies.

During the first year of generic substitution — from April 2003 to March 2004 — there were a total of 12.4 million prescriptions filled for substitutable medicines dispensed by pharmacies and refunded by the health insurance scheme. This is about 45% of all refunded prescriptions during that time, i.e. purchase of a medicine prescribed by a doctor.

The proportionate cost of substitutable drugs among the total costs of all refunded drugs during the year was about 34%. In April 2003, the proportion was 36% and in March 2004 it was less than 33%. This fluctuating percentage can be explained by the increasing use of more recently marketed expensive drugs and by price reductions affecting substitutable products. An increase may also be felt, of course, as more medicinal

Table 1. Prescriptions, costs and savings of substitutable products reimbursed by the national health insurance scheme (1 April 2003 to 31 March 2004).

	Prescriptions		Costs		Cost savings	
	000s	share%	000s	share%	000s	share%
A Alimentary tract and metabolism	648	5.2	28 650	5.0	3650	4.1
B Blood and blood forming organs	45	0.4	1553	0.3	16	0.0
C Cardiovascular system	4604	37.1	197 790	41.0	46 941	53.2
D Dermatologicals	120	1.0	11 882	2.5	1225	1.4
G Genito urinary system and sex hormones	512	4.1	28 984	6.0	2376	2.7
H Systemic hormonal preparations	47	0.4	1215	0.3	5	0.0
J Antiinfectives for systemic use	2013	16.2	39715	8.2	7377	8.4
L Antineoplastics and immunomodulating agents	144	1.2	23 880	5.0	304	0.3
M Musculo-skeletal system	1508	12.2	34760	7.2	4443	5.0
N Nervous system j	1958	15.8	86 994	18.1	17 434	19.7
P Antiparasitic products, insecticides and repellants	20	0.2	268	0.1	23	0.0
R Respiratory system	680	5.5	23 914	5.0	3846	4.4
S Sensory organs	92	0.7	2214	0.5	660	0.7
All substitutable products	12 394	100.0	481 829	100.0	88 300	100.0

Source: Prescription Register at Kela

substances become substitutable on patent expiry. Medicines used for cardiovascular diseases accounted for about 40% of all prescriptions and costs of substitutable drugs (Table 1). Measured by the number of prescriptions, the biggest groups thereafter were anti-infectives and drugs for the treatment of the nervous system.

During the year, about one in eight prescriptions for a substitutable drug was replaced by a cheaper alternative by the pharmacy. The most common substitutions made were of antihistamines (30% of prescriptions), antidepressants (27%) and lipid-lowering agents (23%). Substitutions were forbidden by prescribers in only 0.4% of substitutions, and clients declined a substitution in less than 11 % of cases. In nearly three out of four prescriptions, the prescribed product was already within the price corridor, in which case there was no need to replace it.

Cost savings

The total savings generated during the first year of generic substitution in Finland amounted to 88.3 million, which is about 6% of the total costs of drugs refunded from the health insurance system during the same period. The clients' proportion of the sum was 39.2 million, and the savings in reimbursement costs payable by the Social Insurance Institution totalled 49.1. The proportion for health insurance is higher than that for clients' mainly because a great number of

drugs entitled to special reimbursement fall into the category of generic substitution. Over half of the total savings were generated by drugs used for cardiovascular diseases (Table 1). The proportion of the total savings due to substitution was about a third, 28.8 million.

Over half of the savings created by generic substitution came from substituting lipid-lowering agents and antidepressants (Table 2). The cost saving for each substitution was on average 18.39. One substitution involving the product citalopram saved almost 56, and that of the product simvastatin about 47. Other drug groups where substitutions created significant savings were, for example, beta blockers and ACE inhibitors.

The greatest cost saving — two-thirds of total costs — was created through price reductions from tougher price competition. The calculations do not, however, take into account any price changes or generic substitutions in those substitutable drugs which were not eligible for a refund from the health insurance system. Consequently, the actual savings may well be even higher than calculated.

Generic substitution reduced the rate of refunds during 2003. The cost of refunds from the health insurance system, totalling 917.5 million,

Table 2. Drug groups and medicines eligible for reimbursement which generated the most savings through generic substitution (1 April 2003 — 31 March 2004)

	Cost savings 000s	Cost savings/exchange Share %	
C10 Serum lipid reducing agents	7970	27.7	44.59
Sim vasta tin	7613	26.5	47.16
Lovastatin	370	1.3	27.51
N06 Psychoanaleptics	7905	27.5	43.98
Citalopram	7312	25.4	55.78
Paroxetin	400	1.4	15.91
C07 Beta blocking agents	4055	14.1	15.77
Bisoprolol	2877	10.0	15.98
Atenolol	900	3.1	23.81
C09 Agents acting on the renin-angiotensin system	3488	12.1	26.08
Enalapril	2398	8.3	29.39
Enalapril and diuretics	624	2.2	23.15
Lisinopril	451	1.6	23.94
R06 Antihistamines for systemic use	1242	4.3%	12.31
Cetirizin	790	2.7	11.13
Loratadin	452	1.6	15.10
J01 Antibacterials for systemic use	1107	3.8	8.88
Ciprofloxacin	878	3.1	22.45
J02 Antimycotics for systemic use	756	2.6	8.89
Fluconazole	756	2.6	8.89
G04 Urologicals	583	2.0	14.42
Finasteride	495	1.7	16.81
All substitutable products	28.759	100.0	18.39

Source: Prescription Register at Kela

increased by less than 7% compared with the previous year, whereas the increase in 2002 was about 12 % over the previous year. Price reductions of substitutable drugs and a raised top limit of fixed co-payment from 8.40 to 10 in the basic refund category placed several less expensive drugs outside the refunding system altogether, e.g. some anti-inflammatory analgesics and antibiotics. The number of patients receiving refunds did in fact drop by about 2 % in 2003 compared with the previous year.

In conclusion, the first year of generic substitution exceeded all expectations. Clients have in the main been satisfied with the new procedure, and considerable savings have been generated by the system. The price of individual substitutable

products was reduced by a maximum of 80% in comparison with prices prior to the introduction of generic substitution. In the future, the extent of generated savings and the growth rate of medicine costs will be dependent on such factors as the number of medicinal substances falling in the category for generic substitution, and the overall value of sales.

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Safety and Efficacy Issues

Australian experience with pneumococcal conjugate vaccine

Pneumococcal conjugate vaccine was registered in February 2001 for active immunization of infants and children from 6 weeks to 9 years of age against invasive disease, pneumonia and otitis media caused by *Streptococcus pneumoniae*. From surveys conducted, the seven serotypes included in the vaccine will cover about 85% of invasive isolates in urban Australian children and 67% of invasive isolates in indigenous Australian children (1). In a clinical trial of infant immunization, efficacy against invasive pneumococcal disease caused by vaccine serotypes of *S. pneumoniae* was 97% (2).

Commencing on 1 January 2005, a new Universal Childhood Pneumococcal Vaccination Program will provide free pneumococcal conjugate vaccine for all children at 2, 4 and 6 months of age, plus catch-up vaccination in 2005 for all children under 2 years of age (3). Up to March 2004, 52 000 first doses, 32 000 second doses and 20 000 third doses of pneumococcal conjugate vaccine had been administered to children under 7 years who had met the current criteria for funded vaccination (4).

The Australian Adverse Drug Reactions Committee (ADRAC) has received 41 reports related to pneumococcal conjugate vaccine (sole suspected agent in 23 cases). The most common reactions include: pyrexia (8), injection site reaction (8), and vomiting (5). There were 2 reports of lack of efficacy. In the first case, a 2-year-old child developed pneumococcal pneumonia with serotype 6B, two months after being given a single dose. In the second case, a 7 month old female who had received her third dose four months previously developed serotype 18C pneumococcal infection with bacteraemia. Both children recovered.

Reassuringly, no major or unexpected adverse events have been reported in association with the use of pneumococcal conjugate vaccine in Australian children.

Extracted from: Australian Adverse Drug Reactions Bulletin, Volume 23, Number 5, October 2004.

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2. Black, S., Shinefield, H., Fireman, B. et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatric Infectious Diseases Journal*, **19**: 187-195 (2000).
3. National Childhood Pneumococcal Vaccination Program. Department of Health and Ageing. 19 July 2004. <http://www.immunise.health.gov.au/pneumococcal/index.htm>
4. Australian Childhood Immunisation Register. HIC Statistical Reporting, Health Insurance Commission. http://www.hic.gov.au/providers/health_statistics/statistical_reporting/acir.htm

Overdose and tricyclic antidepressants

The total quantity in milligrams of tricyclic antidepressant that can be obtained by patients at risk of suicide is a concern. Particularly, high-dose presentations of tricyclic antidepressants have been associated with patient deaths from overdose. An overdose of dothiepin may be more likely to be fatal than overdoses of other tricyclic antidepressants (1).

Approved indications for the 50 mg and 75 mg tricyclic antidepressant presentations have been changed to limit use to maintenance treatment, in an attempt to reduce the risk of suicide in acutely depressed patients. The product information for these high dose products now warns of the risk of suicide by overdose. These products remain available for the treatment of major depression, but prescribers should limit prescriptions of high dose (i.e. 50 and 75 mg) tricyclic antidepressants to patients who have recovered beyond acutely depressed or suicidal phases.

Extracted from: Australian Adverse Drug Reactions Bulletin, Volume 23, Number 5, October 2004.

Reference

1. Buckley, N.A., Dawson, A.H., Whyte, I.M. et al. Greater toxicity in overdose of dothiepin than of other tricyclic antidepressants. *Lancet*, **343**: 159–162 (1994).

Terbinafine and blood dyscrasias

Oral terbinafine is indicated for onychomycosis caused by dermatophyte fungi and for tinea unresponsive to topical therapy. Haematological reactions, notably agranulocytosis, neutropenia or pancytopenia, are rare adverse effects of systemic terbinafine therapy. Onset is commonly within 4–6 weeks after commencing therapy and resolution may occur within a week if terbinafine is stopped promptly (1–6).

The Australian Adverse Drug Reactions Committee (ADRAC) has received 14 reports of blood dyscrasias with oral terbinafine (total reports 534): agranulocytosis, neutropenia or pancytopenia. The age range was 35 to 84 years. Some patients with terbinafine-associated low white cell counts have developed multisystem involvement with rash and hepatic impairment, suggestive of a drug hypersensitivity syndrome (6). Patients taking terbinafine for longer than a month should be advised to report any symptoms of possible infection, such as fever or sore throat. Blood counts should be checked if symptoms develop.

Other reactions associated with oral terbinafine reported to ADRAC (7) include taste perversion (143 reports), abdominal pain or discomfort, nausea, hepatic dysfunction, (including one death) and serious skin reactions.

Extracted from: Australian Adverse Drug Reactions Bulletin, Volume 23, Number 5, October 2004.

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Cholinesterase inhibitors and cardiac arrhythmias

Cholinesterase inhibitors such as donepezil, rivastigmine and galantamine are being used increasingly in the treatment of Alzheimer's disease. The product information for all three drugs notes that increased cholinergic activity may have vagal effects on heart rate such as bradycardia.

The Table below shows reports of cardiac arrhythmias and other effects, like syncope, which may be indicative of such problems. The larger

Table: Cardiac arrhythmias with cholinesterase inhibitors

	Donepezil	Rivastigmine	Galantamine
Bradycardia	14	7	6
Bundle branch block	1	-	1
AV block	5	-	1
Syncope	10	8	4
Unspecified arrhythmia	2	-	1
Myocardial infarction/cardiac arrest	7	1	-
Total number of all reports	235	82	54
PBS prescriptions (to December 2003)	439 000	78 000	67 000

number of reports with donepezil is almost certainly due to greater usage of this drug. Most patients recovered after the cholinesterase inhibitor was stopped or in some cases, reduced in dose. Many patients were hospitalized, and in 4 cases a pacemaker was required. Four elderly patients died from suspected myocardial infarction; it is unclear whether their medication had any role in these events.

Prescribers need to be aware of the potential for cardiac arrhythmias, particularly bradycardia, with cholinesterase inhibitors. Patients with sick sinus syndrome or other supraventricular cardiac conduction conditions may be at particular risk. A pharmacodynamic interaction can also be predicted with the concomitant use of beta-blockers or calcium channel blockers.

Extracted from: Australian Adverse Drug Reactions Bulletin, Volume 23, Number 5, October 2004.

Lamotrigine: hormonal contraceptives decrease serum levels

Canada — The manufacturer of lamotrigine (Lamictal®), an anti-epileptic, has announced important new safety information concerning concomitant use of hormonal contraceptives with lamotrigine, which may significantly decrease serum lamotrigine levels. There have also been a limited number of post-marketing reports of breakthrough seizures occurring with the concomitant use of lamotrigine and hormonal preparations. Significant adjustments in the maintenance dose may be required in some patients. Patients should be advised not to start or stop their oral contraceptives without consulting their physician.

Lamotrigine has a modest effect on levonorgestrel plasma concentrations and a minimal effect on ethinylestradiol concentrations. However, a limited number of reports have been received of unexpected pregnancies and of menstrual bleeding disorders (e.g. breakthrough bleeding) occurring with the concomitant use of lamotrigine and hormonal preparations. Women should be advised to promptly notify their physician if they experience changes in menstrual pattern (e.g., breakthrough bleeding).

The effect of other hormonal contraceptive preparations or hormone replacement therapy (HRT) on the pharmacokinetics of lamotrigine has not been evaluated, although the effect may be

similar to oral contraceptive preparations, and as such, dosage adjustments may be necessary.

A recently completed clinical pharmacology study, in healthy human volunteers, investigating the interaction between lamotrigine 300 mg once daily and an oral contraceptive preparation containing 30 µg ethinylestradiol and 150 µg levonorgestrel has documented that:

- An oral contraceptive preparation administered in combination with lamotrigine significantly decreased serum levels of lamotrigine (on average, 52% decrease in AUC and 39% decrease in C_{max})
- During the “pill-free” week of the oral contraceptive there was a gradual increase in trough lamotrigine serum concentrations, by approximately two fold by the end of the “pill-free” week.
- Lamotrigine had a modest effect on levonorgestrel plasma concentrations (on average, 19% decrease in AUC and 12% decrease in C_{max}). The effect on ethinylestradiol concentrations was minimal.
- An increase in serum FSH and LH concentrations and a marginal increase in serum estradiol concentrations were observed during the period of co-administration of the oral contraceptive and lamotrigine
- There was no hormonal evidence of ovulation as evidenced by progesterone serum concentrations.
- The manufacturer has received a limited number of reports of breakthrough seizures, unexpected pregnancies and of menstrual bleeding disorders (e.g. breakthrough bleeding) occurring with the concomitant use of lamotrigine and hormonal preparations.

The product monograph will be revised to reflect the results of this study including recommendations for the use of Lamictal® in women taking oral contraceptives. Women should also be advised to notify their physician if they plan to start or stop use of oral contraceptives or other hormonal preparations or if they experience changes in menstrual pattern (e.g., breakthrough bleeding).

Reference: Communication from GlaxoSmithKline Inc., September 2004 on <http://www.hc-sc.gc.ca>

Transdermal fentanyl and respiratory arrest in adolescents

Health Canada has received two case reports of death suspected of being associated with the use of transdermal fentanyl system (Duragesic®) prescribed off-label to adolescents. In one case, a 15-year-old girl was prescribed Duragesic 25® for chronic headache. She was discovered unresponsive and with respiratory depression 21 hours after the first and only application. She was resuscitated but suffered severe anoxic brain injury and died two days later. In the second case, a 14-year-old boy was prescribed Duragesic 25® for throat pain due to infectious mononucleosis. He was found in respiratory arrest 14 hours after the first and only patch was applied. Resuscitative efforts were unsuccessful.

Duragesic® has been marketed in Canada since 1992 and is indicated for the management of chronic pain in patients requiring continuous opioid analgesia for pain that is not optimally managed with weak or short-acting opioids (1). It is contraindicated for the management of acute or postoperative pain and mild or intermittent pain, and for use in opioid-naïve patients. These contraindications and the risk of serious and life-threatening hypoventilation are well labelled in the Canadian product monograph. Use in children under 18 years of age is not recommended in Canada (1).

A thorough understanding of the pharmacokinetics and delivery system is essential to the safe prescribing of this product. The transdermal therapeutic system allows the continuous delivery of the opioid analgesic fentanyl for up to 72 hours (1). It is a transparent patch comprised of a protective peel strip and 4 functional layers. The protective peel strip is removed before use, and the patch is attached to the skin via a silicone-based contact adhesive, which delivers a loading dose of drug upon application. The fentanyl drug reservoir is located behind a rate-control membrane. The drug diffuses through this membrane and the adhesive to reach the skin. A fentanyl depot accumulates in the upper skin layers, diffuses through to the dermis and is then available for uptake into systemic circulation (2). In adults, the time from application to minimal effective serum concentrations can range from 1.2 to 40 hours, and the time to reach maximum serum concentrations can range from 12 to 48 hours. When the patch is removed, fentanyl continues to be absorbed into the systemic circulation from the cutaneous depot (2). The

serum fentanyl concentrations decline gradually to about 50% in about 17 (range 13-22) hours (1).

In the two cases reported to Health Canada, these opioid-naïve adolescents experienced severe respiratory depression 21 and 14 hours after application of Duragesic 25® and died. Prescribers are reminded that this dosage delivery system for fentanyl is not suitable for acute pain management or for opioid-naïve patients. Patients and their caregivers must be instructed in how to recognize symptoms of serious opioid-related toxicity such as hypoventilation and cognitive impairment (3).

Extracted from Canadian Adverse Reaction Newsletter, Volume 14, Issue 4, October 2004

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Infliximab and etanercept: serious infections and tuberculosis

Tumour necrosis factor-alpha (TNF- α) is a pro-inflammatory cytokine synthesized in response to infectious or inflammatory stimuli (1). TNF- α antagonists have been shown to be effective in the treatment of signs and symptoms of rheumatoid arthritis and other autoimmune diseases (1). Infliximab (Remicade®) is indicated in adults for rheumatoid arthritis (in combination with methotrexate), Crohn disease and fistulizing Crohn disease (2). Etanercept (Enbrel®) is indicated for rheumatoid arthritis in adults and polyarticular juvenile rheumatoid arthritis in patients aged 4 to 17 years (3).

Serious infections, particularly tuberculosis (TB), are recognized risks for patients receiving TNF- α antagonists, and warnings to that effect are prominent in the product monographs (2, 3). Many serious infections have occurred in patients taking immunosuppressive therapy concomitantly, which, in addition to the underlying disease, could predispose them to infections (2, 3).

Table 1: Reports submitted to Health Canada of infections suspected of being associated with infliximab and etanercept from 1 January 2000 to 31 May 2004*

Variable	Infliximab	Etanercept
Total number of AR reports	697	536
Number of AR reports with infection	188	109
Number of AR reports with serious infection (no. of death†)	132 (14)	82 (7)

Note: AR = adverse reaction.

**These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between the products because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.*

† Causality assessment is difficult because of multiple factors such as confounding factors, complexity of the cases as well as the quality and the completeness of the information included in the reports.

Health Canada received a total of 697 reports of suspected adverse reactions (ARs) to infliximab and 536 to etanercept from 1 January 2000 to 31 May 2004 (Table 1). Reports of infection were considered serious when the infection was life threatening or resulted in death, disability, hospital admission or prolonged hospital stay (as defined in the Food and Drug Regulations). The types of serious infections are listed in Table 2. Reports of TB comprised those of new cases (infliximab 3, etanercept 0), reactivation of latent TB (infliximab

3, etanercept 0) and cases in which the patient was prescribed antituberculous medication (infliximab 4, etanercept 2). There were 4 reports of pulmonary or pleural TB (infliximab 4, etanercept 0), 4 reports of extrapulmonary TB (infliximab 4, etanercept 0) and 4 reports in which the type of TB was not specified (infliximab 2, etanercept 2).

A number of registries have been established to assist in assessing the long-term safety and

Table 2: Types of serious infections described in the reports submitted to Health Canada for infliximab and etanercept from 1 January 2000 to 31 May 31 2004*

Type of infection † ‡	Infliximab	Etanercept
Abscess	20	10
Cellulitis	11	3
Encephalitis or meningitis	2	1
Fungal infections	14	2
Pneumonia	36	30
Pyelonephritis or cystitis	7	8
Sepsis	36	15
Septic arthritis	7	4
Tuberculosis	10	2

**These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between the products because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.*

†Because of limited information in the reports, some infections could not be classified and are not included.

‡Several infection types (reaction terms) may be listed per AR report. Reaction terms are based on the World Health Organization Adverse Reaction Dictionary (WHOART).

efficacy of TNF- α antagonists (4, 5). In France the programme is particularly interested in infections and lymphomas (4).

Health care professionals are reminded of the following important safety information included in the Enbrel® and Remicade® product monographs (2, 3).

- Caution should be exercised when considering the use of TNF- α antagonists in patients with chronic infection, a history of recurrent or latent infection, including TB, or an underlying condition that may predispose them to infection.
- TNF- α therapy should not be initiated in patients with a clinically important, active infection.
- New infections should be closely monitored and therapy discontinued if the infection becomes serious.

Patients should be instructed in how to recognize early signs and symptoms of infection and be advised to seek medical attention when they occur.

Extracted from Canadian Adverse Reaction Newsletter, Volume 14, Issue 4, October 2004

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Medication error alert

Manufacturers have recently been made aware of several reports of medication errors involving confusion between Reminyl® (galantamine hydrobromide), a drug approved for the treatment of mild to moderate dementia of the Alzheimer's type, and Amaryl® (glimepiride), indicated for the treatment of non-insulin-dependent (Type 2) diabetes mellitus. These reports include instances in which Reminyl was prescribed but Amaryl was incorrectly dispensed and administered instead, leading to various adverse events including severe hypoglycaemia and one death.

According to the spontaneous reports submitted to the Food and Drug Administration and the United States Pharmacopoeia, prescriptions have been incorrectly written, interpreted, labelled, and/or filled due to the similarity in names between Reminyl and Amaryl. These two products have an overlapping strength (4 mg) and an overlapping dosage form (tablets). In addition, both products have generic names (galantamine vs glimepiride) that might lead to their storage in close proximity.

Reference: Reminyl Prescribing Information, Janssen Pharmaceutica Products, L. P. March 2003 and Amaryl Prescribing Information, Aventis Pharmaceuticals Inc. August 2004 on <http://www.fda.gov/medwatch>

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.

Current Topics

International standard for genetic testing

The first international standard for a human genetic test has been approved by the WHO Expert Committee on Biological Standardization. Use of the standard will help to improve the accuracy and quality of laboratory results for a genetic test which identifies a predisposition to thrombosis. The newly established International Reference Panel relates to the genetic mutation known as Factor V Leiden. Discovered in 1994, this mutation is one of the most common genetic risk factors for venous thrombosis, and is involved in 20–40% of all cases.

Factor V Leiden induces a defect in the natural anticoagulation system. Researchers are currently investigating whether or not there is a link between air travel and deep vein thrombosis. This is one example of a condition which may result from the Factor V Leiden mutation. Having information about genetic make-up could allow travellers at risk to take additional precautions.

The test for Factor V Leiden is one of the most frequent genetic tests carried out in clinical laboratories to determine the presence or absence of the mutation, which has been shown to result in a seven-fold to 80-fold higher risk of thrombosis depending on whether the individual carries one or two copies of the gene respectively.

The new standard was agreed at the 55th session of the WHO Expert Committee on Biological Standardization (ECBS) which met from 15 to 18 November in Geneva. It is composed of ten global experts from academia, industry and national regulatory authorities, as well as 25 advisors. A key function of WHO is to develop, establish and promote international standards with respect to biological and other products. WHO is the world authority on biological standards, and has established more than 300 standards covering vaccines; blood products; therapeutic biological products, such as insulin; and diagnostic tests, such as those that detect HIV in a blood product.

DNA-based genetic testing offers promise for improved disease management by giving doctors

better information about patients on which to base diagnosis and treatment or counselling. It also offers the potential for better targeting of therapies and drugs to those patients most likely to benefit. Hundreds of different genetic tests are currently available.

A recent study estimated that in the European Union alone more than 700 000 genetic tests were performed in 2002; and found that at least 700 laboratories and 900 clinical centres in Europe were carrying out genetic tests (2). Though the exact number is unknown, it is likely that millions of genetic tests are being carried out worldwide each year. Genetic testing must be conducted in a consistent manner in all laboratories around the world and to high quality standards in order to give confidence in the results.

Once a WHO collaborating laboratory physically creates a standard, it is typically evaluated by 15 other top laboratories. The ECBS reviews the laboratory data and decides to approve or not the proposed standard for international use. The rigorous assessment of the standard for the Factor V Leiden genetic test was carried out by an international panel of investigators in conjunction with the International Society on Thrombosis and Hemostasis (ISTH).

References

1. <http://www.who.int>. Press release, 17 November 2004.
2. Ibarreta, D., Elles, R., Cassiman, J-J. et al. Towards quality assurance and harmonization of genetic testing services in the European Union. *Nature Biotechnology*, **22**: 1230–1235 (2004).

Selective reporting and clinical trial registration

A statement recently appeared in the *New England Journal of Medicine* by members of the International Committee of Medical Journal Editors concerning the proposed policy on acceptance of publications and clinical trial registration. The text is reproduced below and the

conditions of the policy are set out on the following pages.

“Altruism and trust lie at the heart of research on human subjects. Altruistic individuals volunteer for research because they trust that their participation will contribute to improved health for others and that researchers will minimize risks to participants. In return for the altruism and trust that make clinical research possible, the research enterprise has an obligation to conduct research ethically and to report it honestly. Honest reporting begins with revealing the existence of all clinical studies, even those that reflect unfavourably on a research sponsor’s product.

“Unfortunately, selective reporting of trials does occur, and it distorts the body of evidence available for clinical decision-making. Researchers (and journal editors) are generally most enthusiastic about the publication of trials that show either a large effect of a new treatment (positive trials) or equivalence of two approaches to treatment (non-inferiority trials). Researchers (and journals) typically are less excited about trials that show that a new treatment is inferior to standard treatment (negative trials) and even less interested in trials that are neither clearly positive nor clearly negative, since inconclusive trials will not in themselves change practice. Irrespective of their scientific interest, trial results that place financial interests at risk are particularly likely to remain unpublished and hidden from public view.

“The interests of the sponsor or authors notwithstanding, anyone should be able to learn of any trial’s existence and its important characteristics. The case against selective reporting is particularly compelling for research that tests interventions that could enter mainstream clinical practice. Rather than a single trial, it is usually a body of evidence, consisting of many studies, that changes medical practice. When research sponsors or investigators conceal the presence of selected trials, these studies cannot influence the thinking of patients, clinicians, other researchers, and experts who write practice guidelines or decide on insurance-coverage policy. If all trials are registered in a public repository at their inception, every trial’s existence is part of the public record and the many stakeholders in clinical research can explore the full range of clinical evidence. We are far from this ideal at present, since trial registration is largely voluntary, registry data sets and public access to them varies, and registries contain only a small proportion of trials.”

Reference: Catherine De Angelis, Jeffrey M. Drazen, Frank A. Frizelle, Charlotte Haug, John Hoey, Richard Horton, Sheldon Kotzin, Christine Laine, Ana Marusic, A. John P.M. Overbeke, Torben V. Schroeder, Hal C. Sox, and Martin B. Van Der Weyden. *New England Journal of Medicine*, 351:1250–1251 (2004).

Trials registration policy

The International Committee of Medical Journal Editors (ICMJE) proposes comprehensive trials registration as a solution to the problem of selective awareness and announces that all ICMJE member journals will adopt a trials-registration policy to promote this goal. The member journals are: *Journal of the American Medical Association*, *New England Journal of Medicine*, *The New Zealand Medical Journal*, *Norwegian Medical Journal*, *Canadian Medical Association Journal*, *The Lancet*, *Annals of Internal Medicine*, *Croatian Medical Journal*, *Nederlands Tijdschrift voor Geneeskunde*, *Journal of the Danish Medical Association*, *The Medical Journal of Australia* and the *US National Library of Medicine*.

The ICMJE member journals will require, as a condition of consideration for publication, registration in a public trials registry. Trials must register at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after 1 July 2005. For trials that began enrollment before this date, the ICMJE member journals will require registration by September 13, 2005, before considering the trial for publication. We speak only for ourselves, but we encourage editors of other biomedical journals to adopt similar policies. For this purpose, the ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., phase 1 trials), would be exempt.

The ICMJE does not advocate one particular registry, but its member journals will require authors to register their trial in a registry that meets several criteria. The registry must be accessible to the public at no charge. It must be open to all prospective registrants and managed by a not-for-profit organization. There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable. An acceptable registry must include

at minimum the following information: a unique identifying number, a statement of the intervention (or interventions) and comparison (or comparisons) studied, a statement of the study hypothesis, definitions of the primary and secondary outcome measures, eligibility criteria, key trial dates (registration date, anticipated or actual start date, anticipated or actual date of last follow-up, planned or actual date of closure to data entry, and date trial data considered complete), target number of subjects, funding source, and contact information for the principal investigator. To our knowledge, at present, only www.clinicaltrials.gov, sponsored by the United States National Library of Medicine, meets these requirements; there may be other registries, now or in the future, that meet all these requirements.

Registration is only part of the means to an end; that end is full transparency with respect to performance and reporting of clinical trials. Research sponsors may argue that public registration of clinical trials will result in unnecessary bureaucratic delays and destroy their competitive edge by allowing competitors full access to their research plans. We argue that enhanced public confidence in the research enterprise will compensate for the costs of full disclosure. Patients who volunteer to participate in clinical trials deserve to know that their contribution to improving human health will be available to inform health care decisions. The knowledge made possible by their collective altruism must be accessible to everyone. Required trial registration will advance this goal.

Reference: Catherine De Angelis, Jeffrey M. Drazen, Frank A. Frizelle, Charlotte Haug, John Hoey, Richard Horton, Sheldon Kotzin, Christine Laine, Ana Marusic, A. John P.M. Overbeke, Torben V. Schroeder, Hal C. Sox, and Martin B. Van Der Weyden. *New England Journal of Medicine*, **351**:1250–1251 (2004).

National Library of Medicine trials registration

As a consequence of the International Committee of Medical Journal Editors (ICMJE) statement on trials registration, concerns have been raised that ClinicalTrials.gov is the only existing registry that currently fulfils the ICMJE specified criteria for acceptable registries. Although ClinicalTrials.gov includes numerous trials that have sites outside the USA (about 90 countries are represented in the registry), at the time of the statement, the registry was open only to US government-

sponsored trials or to multisite studies sponsored by companies applying for FDA approval that include locations outside of the United States.

Consequently, many investigators who wish to register their trials did not have an acceptable registry available to them. Fortunately, the National Library of Medicine (NLM) agrees to accept validated descriptions of all clinical trials without charge from the international community for inclusion in ClinicalTrials.gov. The NLM and ICMJE concur that the validation of trial registry data is essential. The absence of a mechanism for this validation has previously been an obstacle to universal registration of trials in ClinicalTrials.gov. In order to ensure current and accurate information for each trial, the NLM will ask those registering trials to adhere to strict submission and update procedures.

NLM will look to national and international health authorities to support the validation of the descriptions of clinical trials originating within their domains. In the initial phase of registering trials from all parts of the world, the NLM will recognize and display some trials as pending receipt of validation of the description and official local acknowledgement of the existence of the trial by the relevant national or international health authority. The NLM will keep such listings up to date as they receive notification of approvals and validation from the registrant organization.

From the committee's perspective the most critical issues regarding the acceptability of registries are that the price to register or to use the registry is not a barrier to anyone, that the registry will not simply vanish when it becomes inconvenient or financially untenable, and that the registry management is in some form accountable to the public for the conduct of the registry. The ICMJE anticipates that existing registries that currently do not meet the criteria for registries acceptable to the ICMJE may undergo changes to become acceptable. In addition, new registries may develop.

The ICMJE remains confident that the many recent forces promoting trials registration will soon result in the public having better access to information about the investigation of medical interventions than it has now.

Reference: Update statement from the ICMJE on <http://www.icmje.org>

Regulatory and Safety Action

Antidepressants and suicidality in children and adolescents

United States of America — the Food and Drug Administration (FDA) has directed manufacturers of all antidepressant drugs to revise the labelling for their products to include a boxed warning and expanded warning statements that alert health care providers to an increased risk of suicidality (suicidal thinking and behaviour) in children and adolescents, and to include additional information about the results of paediatric studies. FDA also informed these manufacturers that a patient medication guide should be provided to patients receiving the drugs to advise them of the risks and precautions to be taken. These labelling changes follow recommendations of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Drugs Advisory Committee.

The drugs that are the focus of this new labelling are:

Anafranil® (clomipramine HCl); Aventyl® (nortriptyline HCl); Celexa® (citalopram HBr); Cymbalta® (duloxetine HCl); Desyrel® (trazodone HCl); Effexor® (venlafaxine HCl); Elavil® (amitriptyline HCl); Lexapro® (escitalopram oxalate); Limbitrol® (chlorthalidazine/amitriptyline); Ludiomil® (Maprotiline HCl); Luvox® (fluvoxamine maleate); Marplan® (isocarboxazid); Nardil® (phenelzine sulfate); Norpramin® (desipramine HCl); Pamelor® (nortriptyline HCl); Parnate® (tranylcypromine sulfate); Paxil® (paroxetine HCl); Pexeva® (paroxetine mesylate); Prozac® (fluoxetine HCl); Remeron® (mirtazapine); Sarafem® (fluoxetine HCl); Serzone® (nefazodone HCl); Sinequan® (doxepin HCl); Surmontil® (trimipramine); Symbyax® (olanzapine/fluoxetine); Tofranil® (imipramine HCl); Tofranil-PM® (imipramine pamoate); Triavil® (Perphenazine/Amitriptyline); Vivactil® (protriptyline HCl); Wellbutrin® (bupropion HCl); Zoloft® (sertraline HCl); Zyban® (bupropion HCl).

The risk of suicidality for these drugs was identified in a combined analysis of short-term (up to 4 months) placebo-controlled trials of nine antidepressant drugs, including selective serotonin

reuptake inhibitors (SSRIs) and others, in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders. A total of 24 trials involving over 4400 patients were included. The analysis showed a greater risk of suicidality during the first few months of treatment in those receiving antidepressants. The average risk of such events was 4%, twice the placebo risk of 2%. No suicides occurred in these trials. Based on these data, FDA has determined that the following points are appropriate for inclusion in the boxed warning:

- Antidepressants increase the risk of suicidal thinking and behaviour (suicidality) in children and adolescents with MDD and other psychiatric disorders.
- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behaviour.
- Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.
- A statement regarding whether the particular drug is approved for any paediatric indication(s) and, if so, which one(s).

Among the antidepressants, only fluoxetine is approved for use in treating MDD in paediatric patients. fluoxetine, sertraline, fluvoxamine, and clomipramine are approved for OCD in paediatric patients. None of the drugs is approved for other psychiatric indications in children.

Paediatric patients being treated with antidepressants for any indication should be closely observed for clinical worsening, as well as agitation, irritability, suicidality, and unusual changes in behaviour, especially during the initial few months of a course of drug therapy, or at times of dose

changes, either increases or decreases. This monitoring should include daily observation by families and caregivers and frequent contact with the physician. It is also recommended that prescriptions for antidepressants be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

In addition to the boxed warning and other information in professional labelling on antidepressants, MedGuides are being prepared for all antidepressants to provide information about the risk of suicidality in children and adolescents. MedGuides are intended to be distributed with each prescription or refill of a medication.

Reference: *FDA Public Health Advisory*, 15 October 2004 and <http://www.fda.gov/cder/drug/antidepressants/default.htm>.

Withdrawal of rofecoxib

United States of America — Rofecoxib (Vioxx®), a prescription COX-2 selective nonsteroidal anti-inflammatory drug (NSAID), has been voluntarily withdrawn from the market by the manufacturer due to safety concerns. Rofecoxib was approved by the Food and Drug Administration (FDA) in May 1999 for the relief of signs and symptoms of osteoarthritis, for the management of acute pain in adults, and for the treatment of menstrual symptoms. It is also approved for the relief of the signs and symptoms of rheumatoid arthritis in adults and children.

The Data Safety Monitoring Board of an ongoing long-term study of rofecoxib (APPROVe) had recommended that the study be stopped early for safety reasons. The study was being conducted in patients at risk for developing recurrent colon polyps, and showed an increased risk of cardiovascular events (including heart attack and stroke) in patients on Vioxx® compared to placebo, particularly those who had been taking the drug for longer than 18 months.

The risk that an individual patient taking rofecoxib will suffer a heart attack or stroke related to the drug is small. Patients who are currently taking rofecoxib should contact their physician for guidance regarding discontinuation and alternative therapies.

References: <http://www.merck.com> and <http://www.fda.gov/cder/drug/infopage/vioxx/default.gov>

European Union — Regulators met with the marketing authorization holder of rofecoxib (Vioxx®), at an informal meeting of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) on 4–5 October 2004 and were updated on the withdrawal of this product.

Rofecoxib (Vioxx®), a cyclo-oxygenase-2 (COX-2) inhibitor, nonsteroidal anti-inflammatory medicine (NSAID) was first authorized in the United Kingdom in 1999, and thereafter in EU Member States through the mutual recognition procedure. It is used as a treatment for osteoarthritis, rheumatoid arthritis, with higher dose-strengths indicated for short-term relief of acute pain.

The EU regulators agreed to review available long-term data on cardiovascular safety for all licensed COX-2 inhibitors (celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib) in the next two weeks. Based on this review, the Pharmacovigilance Working Party and the CHMP will discuss whether further action is needed. The European Medicines Agency (EMA) has previously reviewed the class of COX-2 inhibitors in a formal procedure concluded in November 2003 (a referral under Article 31 of the Community Code on human medicines). This review included safety aspects relating to the stomach, intestine and cardiovascular system (heart and blood vessels) and the skin. Based on data available at the time, the scientific committee considered that the overall benefits of COX-2 inhibitors outweighed the risk of side effects for the target patient population.

There were areas, however that needed to be brought to the attention of prescribers and patients. These related to possible side effects affecting the stomach and intestine, heart and skin. Particular caution was advised for patients who had a known medical history of gastrointestinal or heart problems or who were taking aspirin at the same time. Such patients should be closely followed by prescribers, and treatment adjusted if necessary. The recommendations applied to all substances included in the referral procedure, whether authorized through the centralized procedure (celecoxib, parecoxib and valdecoxib) or through the mutual recognition procedure (celecoxib, etoricoxib and rofecoxib).

Regarding the withdrawal, the following information has now been issued to prescribers.

This product has been withdrawn due to serious thrombotic events. Patients on Vioxx® should be reviewed and alternative treatment considered. When switching patients to other COX-2 inhibitors, prescribers are advised to carefully follow the revised summary of product characteristics (SPC), especially regarding the warnings and precautions in patients with a history of cardiovascular disease.

Reference: EMEA Press Release, 6 October 2004. *EMA statement following withdrawal of Vioxx (rofecoxib)*, EMEA/97949/2004 on <http://www.emea.eu.int> or E-mail: press@emea.eu.int

India — Ranbaxy Laboratories has announced the discontinuation of its rofecoxib formulations with immediate effect from India, Peru, Myanmar and Jordan. All patients who are currently taking these formulations should consult their physicians for alternative medications.

Reference: Press release. Ranbaxy discontinues rofecoxib. New Delhi, 13 October 2004 on <http://www.ranbaxy.com>

Regulations for COX-2 inhibitors

Turkey — The manufacturer of Celebrex® has voluntarily withdrawn its product from the Turkish market on 19 November 2004 after the Turkish Ministry of Health asked for new warnings to be added to the package insert and on the outer package. According to the decision of the Human Medicinal Products Advisory Committee of the European Union regarding COX-2 inhibitors, dated 5 November 2004, new warnings are to be added to the prospectus and on the package of COX-2 inhibitors. The warnings are listed below:

“Additional information to be added to the prospectus: The risk of thrombotic vascular diseases should be clearly defined for patients to be treated with COX-2 inhibitors, particularly in the following situations.

“COX-2 inhibitors should not be used for the treatment of patients who have been diagnosed with active thrombosis (angina pectoris, myocardial infarction, coronary by-pass history of less than one year, stroke, transient ischemic attack, uncontrolled hypertension, congestive heart failure combined with thrombosis)

“When active thrombosis does not exist but there is a congenitally or an acquired thrombosis risk factor. Prophylactic dose of antiaggregant treatment (low doses of acetylsalicylic acid) should be combined, taking into account the gastrointestinal adverse effects of the latter. Patients should be monitored closely for thrombotic vasculopathies.

“No risk of thrombosis. Patients should be warned about the vascular adverse effects of COX-2 inhibitors.

“Notification to be clearly written on the package: “Should not be used by individuals who have obstructive arterial disorder of cardiovascular system, central nervous system or other systems.”

“COX-2 inhibitors should only be prescribed by orthopedic surgeons, rheumatologists, specialists in physical therapy or internal medicine, cardiologists or neurologists. The indication should be identified, and the absence of obstructive arterial disorder or high thromboembolic risk of cardiovascular system, central nervous system or other systems should be verified by a medical committee which should include either a cardiologist or a neurologist.”

Reference: Press Release from the Turkish Ministry of Health, communicated by the President of the Turkish Clinical Pharmacological Society. 11 November 2004.

Southern hemisphere influenza vaccines 2005

World Health Organization — The following influenza virus vaccine composition has been recommended for the forthcoming winter in the southern hemisphere.

- an A/New Caledonia/20/99(H1N1)-like virus;
- an A/Wellington/1/2004(H3N2)-like virus;
- a B/Shanghai/361/2002-like virus (currently used vaccine viruses include B/Shanghai/361/2002, B/Jilin/20/2003 and B/Jisngsu/10/2003).

As in previous years, the national control authorities should approve the specific vaccine viruses used in each country. National public health authorities are responsible for recommendations regarding the use of the vaccine.

Reference: *Weekly Epidemiological Record*, 79: 369–373 (2004).

European regulation for paediatric medicinal products

European Union — Within Europe, more than half of medicines used to treat children have not been tested or authorized for such use. The general lack of information and appropriate formulations for administering medicines to children may well expose children to unforeseen side effects or under-dosing due to a lack of clinical investigation in this population. There is increasing concern within the European Union that the present situation of knowledge in use of paediatric medicines is not sufficient.

In order to address this, the European Commission has recently adopted a collection of measures to increase research, development and authorization of paediatric medicines. Additionally, a paediatric committee has been set up to ensure that medicines developed for children are worthwhile, safe and not duplicative, and based on therapeutic needs.

A proposed *EU Regulation on Medicinal products for Paediatric Use* will require submission of data on medicines for use in children as a condition of marketing authorization application for new products or new indications. These measures should also benefit industry by stimulating innovation of existing products and providing new business opportunities. As a reward for conducting studies, a six month patent extension for the active moiety will be granted. For orphan medicines, a mixed reward and incentive is provided by two years market exclusivity.

With regard to off-patent and generic products, an incentive scheme is proposed for the submission of data on use in children in the form of ten years data protection for new studies granted a paediatric use marketing authorization (PUMA).

Reference: European Union. *Proposal for a Regulation of the European Parliament and of the Council on Medicinal Products for Paediatric Use*. <http://dg3.eudra.org/F2/pharmacos/new.htm>

Ephedrine and pseudoephedrine to become controlled drugs

New Zealand — From 15 October 2004, all ephedrine and pseudoephedrine containing products will become controlled drugs. This means that ephedrine and pseudoephedrine will be controlled under the Misuse of Drugs Act 1975

and the Misuse of Drugs Regulations 1977. Ephedrine will be scheduled as a Class C Part V controlled drug.

Pseudoephedrine will be scheduled as a Class C Part III (partially exempted) controlled drug if it is a cough/cold/flu or decongestant preparation where the package in which the preparation is sold or supplied contains not more than 1.8 grams of pseudoephedrine. If the pseudoephedrine preparation is not described above then it will be scheduled as a Class C Part V controlled drug.

Preparations of pseudoephedrine that are in a modified or sustained release formulation that deliver no more than 240 mg of pseudoephedrine in a 24 hour period will be scheduled as Class C Part V but will be defined as "partially exempted drugs" (and thus still be able to be sold as Class C Part III preparations).

Both ephedrine and pseudoephedrine pose a risk to the public of New Zealand as principal ingredients in the manufacture of the Class A controlled drug methamphetamine, rather than as drugs in their own right.

The classification of ephedrine and pseudoephedrine under the Misuse of Drugs Act will:

- increase legislative controls against the supply and use of these precursor substances;
- give Customs wider powers to investigate importation syndicates, including the ability to conduct controlled deliveries;
- allow for penalties that would be a genuine deterrent to their importation;
- retain the availability of these substances as prescription and pharmacy-only-medicines for legitimate use by the public.

The classification of ephedrine and pseudoephedrine as controlled drugs is considered necessary to tighten up border controls and provide further domestic controls. A licence to import or export controlled drugs must be issued by the Ministry of Health for every consignment containing controlled drugs (including ephedrine and/or pseudoephedrine) that crosses the New Zealand border. Import and export licences are required for all consignments entering or leaving New Zealand from 15 October 2004.

Reference: Communication to all Pharmaceutical Companies and Pharmaceutical Wholesalers, 20 September 2004 on <http://www.medsafe.nz>

Epoetin alfa and blood clot formation in cancer patients

Canada — The manufacturer of epoetin alfa (Eprex®), authorized for use in Canada since 1995 for the treatment of anaemia in patients with cancer, has informed health care professionals of important new safety information.

Results of recent investigational studies have indicated an increased risk of blood clot formation in patients with cancer who were treated with epoetin alfa or erythropoietin products to raise their red blood cells to a level higher than the typical target in this population. In some cases, these blood clots were fatal. Patients with cancer are generally at higher risk of blood clot formation than other patient populations as a result of known risk factors such as cancer itself, chemotherapy and radiation therapy.

Signs and symptoms of blood clot formation include:

- Weakness or numbness of the face, arms or legs and problems with speech or vision which may indicate a stroke (blood clot in the brain);
- Leg swelling, chest pain, shortness of breath or coughing up blood which may indicate a blood clot in the legs or lungs or a heart attack (blood clot in the blood vessels of the heart).

Patients should NOT discontinue their medication without consulting their physician first. As with all medicines, epoetin alfa should not be used by anyone who does not require the drug to treat a disease or its symptoms.

Revised prescribing information in patients with cancer:

- The target haemoglobin concentration should be 120 g/L.
- If haemoglobin increases by more than 10 g/L in a 2-week period or if the haemoglobin exceeds 120 g/L the dose should be reduced by approximately 25%. If the haemoglobin exceeds 130 g/L, doses should be temporarily withheld until the haemoglobin falls to 120 g/L and then reinitiated at the dose approximately 25% below the previous dose.

References

1. Communication from Janssen-Ortho. <http://www.janssen-ortho.com/> and <http://www.hc-sc.gc.ca/> 18 October 2004.

2. FDA Briefing Document for Oncologic Drugs Advisory Committee Meeting (May 4, 2004). *Safety Concerns Associated With Aranesp® (Darbepoetin Alfa) Amgen, Inc. and Procrit® (Epoetin Alfa) Ortho Biotech, L.P., for the Treatment of Anemia Associated With Cancer Chemotherapy*, pages 50, 53, 56. http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037b2_04.pdf

3. Lee, A.Y.Y., Levine, M.N. Venous thromboembolism and cancer: Risks and outcomes. *Circulation*, **107**: 117–121 (2003).

Mifepristone: labelling changes

United States of America —The Food and Drug Administration has announced new safety changes to the labelling of mifepristone (Mifeprex®) approved in 2000 for the termination of early pregnancy, defined as 49 days or less (1). Up to September 2004, approximately 360 000 women have been treated with mifepristone in the USA. However, reports have been received of serious bacterial infection, bleeding, ectopic pregnancies that have ruptured, and death following termination of pregnancy. No causal relationship between these events and the use of mifepristone and misoprostol has been established. However, these reports have led to the revision of the black box labelling and the manufacturer has updated the prescribing information, medication guide and patient agreement (2).

Serious *bacterial infection*, including very rare cases of fatal septic shock have been reported. A sustained fever, severe abdominal pain, or pelvic tenderness in the days after taking mifepristone and misoprostol may be an indication of infection. Atypical presentations of serious infection and sepsis, without fever, severe abdominal pain, or pelvic tenderness, but with significant leukocytosis, tachycardia, or haemoconcentration can occur. No causal relationship between these events and the use of mifepristone and misoprostol has been established.

Vaginal bleeding occurs in almost all patients during the treatment procedure. According to data from trials, women should expect vaginal bleeding or spotting for an average of 9 to 16 days, while up to 8% of all subjects may experience some type of bleeding for 30 days or more.

Prolonged heavy bleeding, defined as soaking through two thick full-size sanitary pads per hour for two consecutive hours, may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention

may be needed to prevent the development of hypovolaemic shock. Patients should seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion. Excessive vaginal bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions.

Mifepristone is contraindicated in patients with a confirmed or suspected ectopic pregnancy and is not effective for terminating these pregnancies. The overall safety and efficacy profile remains unchanged.

References

1. FDA Statement. 15 November 2004. <http://www.fda.gov>
2. Communication from Danco Laboratories, 12 November 2004. <http://www.fda.gov>

TNF-blocking agents and serious infections

United States of America — The manufacturer of adalimumab (Humira®) has communicated new warnings of hypersensitivity reactions and haematologic events, which have been added to the prescribing information. Adalimumab is a biological therapeutic product indicated for the treatment of rheumatoid arthritis.

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another tumour necrosis factor (TNF)-blocking agent, with no added benefit. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from combination of anakinra and other TNF-blocking agents. Therefore, the combination of adalimumab and anakinra is not recommended.

In addition, rare post-marketing reports of anaphylaxis have been received. If an anaphylactic or other serious allergic reaction occurs, administration of adalimumab should be discontinued immediately and appropriate therapy instituted. In clinical trials of adalimumab, allergic reactions overall (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, nonspecified drug reaction, urticaria) have been observed in approximately 1% of patients.

The manufacturer has received infrequent reports of haematologic events, including medically

significant cytopenia with the use of adalimumab, and the FDA has received rare reports of pancytopenia, including aplastic anaemia, with TNF-blocking agents. The causal relationship of these reports remains unclear. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of therapy should be considered in patients with confirmed significant haematologic abnormalities.

Reference: Communication from Abbott Laboratories, on the MedWatch website at www.fda.gov/medwatch. 5 November 2004

Long-term use of Depo-Provera® and bone density loss

United States of America — The Food and Drug Administration (FDA) has announced that a warning will be added to the labelling of Depo-Provera® Contraceptive Injection, an established injectable drug approved for use in women to prevent pregnancy. The warning highlights that prolonged use of the drug may result in significant loss of bone density, and that the loss is greater the longer the drug is administered. This bone density loss may not be completely reversible after discontinuation of the drug. Thus the warning states that a woman should only use Depo-Provera® Contraceptive Injection as a long-term birth control method (for example, longer than two years) if other birth control methods are inadequate for her.

Reference: *FDA Talk Paper*, T04-50. 17 November 2004

Duloxetine approved for neuropathic pain associated with diabetes

United States of America — The Food and Drug Administration (FDA) has announced the approval of duloxetine hydrochloride (Cymbalta®) capsules for the management of pain associated with diabetic peripheral neuropathy. This is the first drug specifically approved for this indication.

Diabetic peripheral neuropathy is a problem associated with long standing diabetes or poor glucose control. Peripheral neuropathy is the most common complication of diabetes mellitus. Diabetic peripheral neuropathy can manifest in a variety of ways but is usually characterized by burning, tingling, and numbing sensations

beginning in the feet, and later affecting the legs and/or hands.

The safety and effectiveness of duloxetine were established in two randomized, controlled studies of approximately 1074 patients. Although the mechanism of action is unknown, patients treated with duloxetine reported a greater decrease in pain compared to placebo. In these trials, 51 percent of patients treated with duloxetine reported at least a 30 percent sustained reduction in pain. In comparison, 31 percent of patients treated with placebo reported this magnitude of sustained pain reduction.

The most commonly reported side effects were nausea, somnolence, dizziness, decreased appetite, and constipation. In some cases, patients experienced dizziness and hot flushes.

Reference: *FDA News*, P04-87. 7 September 2004

Aripiprazole approved for acute bipolar mania

United States of America — The Food and Drug Administration (FDA) has approved aripiprazole (Abilify®) for the treatment of acute bipolar mania, including manic and mixed episodes associated with bipolar disorder.

The approval is based on positive results from two placebo-controlled, three-week trials of 516 hospitalized patients with bipolar 1 disorder who were experiencing an acute manic or mixed episode. In these studies, aripiprazole demonstrated significant improvement in the symptoms of acute manic or mixed episodes.

The most common side effects reported in clinical trials (greater than or equal to 5% incidence and occurred at least twice as frequently in the aripiprazole-treated group compared to the placebo group) were akathisia (an inner sense of restlessness and need to move about), constipation and accidental injury.

Aripiprazole was previously approved by the FDA in 2002 for the treatment of schizophrenia.

Efficacy and tolerability in schizophrenia was established by short-term and longer-term controlled trials. Since its approval, over 2.4 million prescriptions have been written in the United States. Aripiprazole is available on prescription only and is indicated for the treatment of schizophrenia and acute manic and mixed episodes associated with bipolar disorder.

The manufacturer has taken this opportunity to remind users of important safety information concerning conditions associated with antipsychotic medicines. The following effects have been reported:

- A rare but potentially fatal complex of symptoms referred to as neuroleptic malignant syndrome
- Tardive dyskinesia, a condition that can cause potentially irreversible involuntary movements.
- Hyperglycaemia, in some cases extreme and associated with coma or death. It is important that patients tell their healthcare provider if they are diabetic, have risk factors for diabetes (e.g., obesity, family history of diabetes), or if they are experiencing unexpected increases in thirst, urination, or hunger. Before starting treatment with atypical antipsychotics, patients should have their glucose tested and also be monitored during treatment.
- Lightheadedness or faintness (orthostatic hypotension), caused by rising too quickly from a sitting or lying position.
- Other common side effects are: headache, agitation, anxiety, insomnia, nausea, upset stomach, sleepiness, an inner sense of restlessness and need to move about (akathisia), lightheadedness, vomiting, constipation, and tremors.

Reference: Communication from Bristol-Myers Squibb and Otsuka Pharmaceutical, 1 October 2004, on <http://www.Abilify.com>

HIV Medicines

3 by 5 strategy: improving access to paediatric HIV medicines

Antiretroviral (ARV) treatment has become increasingly available over the last decade, transforming HIV disease into a chronic condition, but the widening treatment gap between HIV-infected patients in resource-rich and resource-poor settings has become increasingly unacceptable. In 2003 — of more than 5 million people newly infected with HIV — 700 000 were children. The majority of these children live in subSaharan Africa, with a 95% infection rate attributable to maternal transmission. A fundamental shift to improve access to ARV treatment for resource-poor settings is reflected in action by WHO's 3 by 5 strategy and nongovernmental organization initiatives. Many of these global efforts make clear commitments to securing equitable access for infants and children, but current programmes report that even in successful programmes children are often not included. In 2004, of 12 000 patients on ARVs in projects run by the nongovernmental organization Médecins sans Frontières, only 700 (6%) were children. Meanwhile, the 3 by 5 target aims to ensure 3 million people receive ARV treatment by the end of 2005, but the ultimate success of this strategy will reside on the ability of health programmes to treat infants and children.

Urgent need for paediatric antiretroviral formulations

Current global efforts to scale up access to antiretroviral (ARV) therapy make a clear commitment to improving access for infants and children. However, current programme efforts suggest that paediatric formulations are often not available. Indeed, there is relatively little data to support accurate public health forecasting or estimation of the need for ARVs among HIV-infected children currently needing treatment.

In order to address the urgency of this situation, a technical consultation of over 35 experts was convened in Geneva, 3–4 November 2004, as part of a collaborative effort between WHO, Médecins sans Frontières (MSF), and UNICEF. The aim of the meeting was to review the current status and development of ARVs in HIV-infected infants and young children with the specific intention of identifying immediate steps to increase access to appropriate ARV formulations. Participants were drawn from among paediatricians, clinical nurse specialists, clinical pharmacologists and care-givers involved in the treatment and care of infants and young children infected with HIV; medical and pharmaceutical officers responsible for paediatric HIV treatment and care programmes; technical and medical staff responsible for implementing programmes in UN

agencies, government agencies and nongovernmental organizations; pharmacists or pharmaceutical technology experts; and experts in demand forecasting.

Challenges to treating children

There are many challenges to the treatment of paediatric populations. Although many of the virologic and immunologic principles that underscore the use of antiretroviral therapy are similar for all HIV-infected persons, there are unique considerations for infants and children.

Physiological changes as a consequence of aging produce differences in absorption, distribution, metabolism and excretion of drugs which dictate dosing and treatment options. The dosing must be adjusted as the child grows, and standardized dosing tables must enable health providers to quickly check if the child is in the appropriate dose-range. For smaller children, the drugs need to be palatable, should be stable once mixed (including if mixed with a range of locally available food or drink), and should not have complex food requirements. Methods of dispensing need to be simple and practical, as they are often undertaken by sick parents or other elderly caregivers. All these factors are complicated by the need to use regimens of more than one drug which greatly influences adherence.

Paediatric dosage is generally based on age, weight and/or body surface area, and can therefore be complicated to work out. For example, zidovudine, nevirapine and didanosine for young infants all give dosage requirements for body surface area. This is complicated in resource-poor settings where equipment, facilities and trained staff are limited, and simplified dosage guidance based upon weight and age is urgently required.

Most of the currently available paediatric ARV formulations require children to take large volumes of unpalatable syrups, many of which need cold chain storage and have limited shelf-life and stability after opening. Once children get to 10 or more kilograms in weight, administration becomes more demanding for children and their caregivers. There are still no fixed-dose combinations (FDCs) specifically available for paediatric use. The few children that have access to treatment rely mainly on use of adult capsules or tablets, broken or mixed. This can result in dangerous under- or over-dosing if providers and caregivers do not have proper guidance. Importantly, many of the paediatric ARV formulations that are available are several times more expensive than the adult solid formulations.

A paucity of data reflects the incomplete knowledge of pharmacology of ARVs in children in general. There is clearly marked inter-individual variability, and effects of nutritional status, age, and ethnicity on pharmacokinetics and pharmacodynamics is not well understood or well documented. Even where the first and second line options have been identified, little is known about how many children will tolerate therapy, how long regimens can be expected to last, what second-line regimens to use, and the likely longer term interactions and toxicity. Safety monitoring is also a key issue which has been sadly ignored.

Development of appropriate paediatric formulations

There was agreement at the meeting that although syrups and solutions are the only currently available option for treating infants less than 10 kg, solid formulations are best for treating children over 10 kg. Principles for the use of solid formulations for treating infants and children need to be agreed and standardized with dosing schedules based on a simplified weight chart.

Criteria for optimal paediatric formulations of existing ARVs were discussed and identified,

including a list of selected dual and triple FDCs, and scored single ARV drugs, either originator and/or generics, to simplify treatment for all ages. WHO and other partners were urged to seek dialogue with both originator and generic companies to stimulate production of these formulations.

Current efforts for treatment of infants and children with HIV

Despite the considerable challenges and obstacles discussed and reviewed by the participants, all agreed that children with HIV can be treated successfully but that far greater effort and attention needs to be directed to ensuring that children become a priority as ARV programmes scale up. There are a number of success stories from Botswana, Romania, South Africa and Uganda that could be documented and used for defining best practices.

Participants pointed to four major areas for immediate attention:

- The principles and practice supporting best use of ARVs currently available for paediatric treatment.
- Principles and priorities for the design and development of modified and new appropriate paediatric ARV formulations.
- Demand forecasting and programme indicators for monitoring and evaluating paediatric HIV care and ARV treatment,
- Gaps, obstacles and priority operational research needs.

WHO Prequalification Project

It was recognized that the prequalification project is a very important process in ensuring supply of quality drugs. The project was set up in 2001 as a service provided by WHO to facilitate access to medicines that have been found to meet international standards of safety, quality and efficacy. Participation in the process is voluntary, and innovator or generic companies may submit applications to supply listed products. Applications should contain product specifications, validation, active ingredient (API) and bioequivalence data, and manufacturer's sites have to comply with good manufacturing practices (GMP). In order to stimulate interest in manufacture of paediatric ARV formulations, the prequalification project should issue a request to manufacturers to supply these medicines.

Ensuring availability and use

There are other problems that relate to the ability of programmes to select, procure, supply, store, and distribute paediatric formulations that influence paediatric ARV use in countries. These include.

- Need for supply systems to provide variable small volumes for paediatric use.
- Problems with supplies, shelf-life, distribution and ongoing monitoring of drug quality up to the point of use.
- Complexity of dispensing and use by paediatric patients in community settings.
- The current cost of paediatric formulations, which is significantly higher than prices achieved for adult ARV formulations.
- Lack of demand forecasting which has led to low commercial interest by the pharmaceutical industry in a market perceived as small and high-risk.

It was also recognized that there is a concurrent need for discussion on improving access to HIV-diagnostics for infants and young children.

Key conclusions from the meeting

During the meeting, action was proposed in the following key areas. A full version of the recommendations, including information and background material from the meeting is available on the WHO website at <http://www.who.int/3by5/events/en/>

1. Immediate action

- Harmonized guidance for use of syrups and solid formulations for treating infants and children with currently available products should be provided urgently.
- In order to improve best use of antiretrovirals for paediatric treatment, dosing schedules based on simplified weight-bands and prototype tables should be incorporated into WHO guidance. Such guidance should be the object of regular revision and be available on the WHO website.

2. Development of paediatric formulations

- Criteria for optimal paediatric formulations of existing ARVs were identified and will be circulated for comment prior to publication.
- A list of selected dual and triple FDCs, and scored single ARV drugs from originator and/or generic sources was proposed.

3. Action to increase development, access, production, and licensing

- Incentives for originator or generic manufacturers to develop paediatric dosage formulations should be stimulated. Mechanisms may include public and intergovernmental subsidies for specified research and development, extension of existing public-private partnerships, tax or patent offers or other creative methods.
- Once manufacturers of suitable products have been identified, ways should be examined to expedite WHO prequalification and/or national registration. Paediatric ARV formulations should be considered as priority products for WHO prequalification.
- Dialogue with companies and potential funders should be prioritized to identify needs, stimulate interest in production and facilitate manufacture of paediatric ARV formulations. Development of co-packaged presentations and FDCs should be prioritized.
- The problem of paediatric formulations is not unique to treatment of HIV infection, but is common to other priority diseases such as malaria and tuberculosis. Similar initiatives for paediatric formulations in priority diseases could consolidate market interest.
- Efforts should be made to encourage applications to the prequalification programme by companies wishing to generate product dossiers for paediatric formulations for priority diseases.
- Data on countries with the largest paediatric populations needing treatment with ARVs should be generated and made available to all parties, and particularly manufacturers and producers of ARVs to stimulate production of paediatric formulations.
- WHO should collaborate with relevant regional and national regulatory bodies in order to facilitate regulatory approval of new paediatric ARV formulations, including providing relevant advice on international regulatory requirements, labelling, and paediatric administration.
- There is an urgent need for clinical research of paediatric ARVs, particularly for pharmacokinetic (PK) and bioavailability studies in target populations and the countries where the drugs would be used. Other partners could be approached, e.g. the European and Developing Countries Clinical Trial Partnership (EDCTP) in

order to stimulate research and development by generic and innovator pharmaceutical companies.

- There is a need for more research and data on current practices used in treating infants and on the resulting dosage and bioavailability when adult formulations are crushed and/or capsules opened and mixed with different food stuffs and liquids. WHO and UNICEF should encourage partner organizations to carry out such research.

4. Forecasting and advocacy issues

- UNICEF and WHO need to develop basic tools and indicators to monitor and plan HIV treatment for children, and undertake demand forecasting. These tools will assist countries to set targets for paediatric ARV coverage and estimate market size and production needs.
- Advocacy by all partners at global, regional and national levels is needed to ensure inclusion of children in treatment initiatives; development of suitable paediatric ARVs; reduction in cost of paediatric ARVs; and encouraging alternative methods of drug development.

References

1. UNICEF/MSF/WHO Technical Consultation: Improving access to appropriate paediatric ARV formulations. <http://www.who.int> and crowleys@who.int

2. WHO Treatment guidelines for a public health approach. available at: http://www.who.int/3by5/publications/documents/arv_guidelines/en/

WHO Prequalification: implications of de-listing

The prequalification project was set up in 2001 as a service provided by WHO to facilitate access to medicines used in the treatment of HIV/AIDS, malaria and tuberculosis, that meet unified standards of quality, safety and efficacy. From the outset, UNAIDS, UNICEF, and UNFPA were partners in the project which was also supported by the World Bank as a concrete contribution to the United Nations priority goal of addressing widespread diseases in countries with limited access to quality medicines (1).

In May and August 2004, several products from the Indian manufacturers, Cipla and Ranbaxy, were taken off the prequalified products list following WHO inspections of selected contract

research organizations (CROs) (2). Subsequently, recognizing that there could be problems involving other CROs, WHO sent a letter to all manufacturers in the prequalification process requesting that additional measures be taken to ensure that the bioequivalence studies submitted to WHO meet international standards, including good clinical practices and good laboratory practices. WHO expressed its intent to continue inspecting contract research organizations (CROs) providing data submitted in the prequalification process.

Since this action, WHO has also been informed by the Indian manufacturers Ranbaxy and Hetero of their voluntary withdrawal of several antiretroviral products from the prequalified products list pending submission of new bioequivalence study data. WHO has already been presented with a plan indicating proposed dates for the submission of new study reports by the manufacturers concerned and the first is expected to be completed by December 2004. Meanwhile, two Cipla medicines have been reinstated on the prequalification list following WHO scientific assessment and inspections of study data (3). Other manufacturers have voluntarily withdrawn applications for their products from the prequalification process pending their own internal review of CRO bioequivalence study data.

A recent *Lancet* editorial has underlined the importance of WHO prequalification in ensuring the quality of generic antiretrovirals, and indicating that removals from the prequalification list demonstrate how effective WHO is in taking rapid action when necessary (4). At present, WHO has around 100 applications for generic antiretroviral drugs in the prequalification pipeline.

Current WHO procedures are ultimately improving medicines monitoring mechanisms which will, in the long term, ensure better quality treatment for all patients. Ongoing WHO inspections of CROs conducting tests on antiretrovirals are part of a continuing monitoring process and an integral component of the prequalification work. That work reflects WHO's responsibility to assist countries in promoting quality medicines and improving their quality assurance mechanisms.

The irregularities found during the CRO inspections do not undermine the proven pharmaceutical quality of the medicines, including their purity and stability, but show that not all CROs can be relied upon to adequately conduct studies in accordance with international standards.

The best course of action

In principle, patients should suspend the use of de-listed medicines and switch to other prequalified products. However, in many cases it will be difficult to find alternative prequalified products immediately. In addition, the risk of withholding treatment is considered higher than that of providing medicines which have in all other respects been prequalified, but do not have confirmed bioequivalence.

Information on the practical implications of the withdrawal of the above-mentioned products from the list of prequalified products for treatment programmes can be accessed on the WHO prequalification project website, where a list of alternative prequalified products is available (<http://mednet3.who.int/prequel/>). Users are reminded that responsibility for authorizing marketing and use of medicinal products in public health programmes rests with the national drug regulatory authority (See recommended action for regulators below).

When deciding on the best course of action, national authorities, programmes, prescribers and patients should take the following overall considerations into account:

- These products may or may not be bioequivalent; and
- Interruption of ARV treatment constitutes a serious risk for the individual and may have negative implications from a public health perspective.

Recommended action for regulators

As a general rule, many national drug regulatory authorities do not require bioequivalence data to admit generic drugs onto their markets. If this is the case, there is no legal obligation to withdraw marketing authorization for the withdrawn products. In countries where bioequivalence is required, the national drug regulatory authority should consider one or more of the following actions:

1. Temporarily waive its requirement of bioequivalence for these products as an emergency measure, requesting that the manufacturers submit data on new bioequivalence studies within four months (if these deadlines are not met, consider withdrawing marketing authorization).

2. Do not release the products in stock for use until further evidence from new bioequivalence studies becomes available.

3. Withdraw marketing authorization for the products.

4. Provide detailed information and advice to programme managers, prescribers and patients on the best ways to manage the situation without compromising the goals of treatment programmes.

Practical implications for health programmes

In all cases, a careful balance must be sought between the risks associated with the lack of proof of bioequivalence in these products and the individual and public health risk of interrupting treatment should no alternative medicines be found. In general, switching to similar antiretrovirals (ARVs) from alternative, prequalified suppliers would be the most appropriate response, if and when such products are available.

However, switching to non-prequalified ARVs is not advisable since neither the bioequivalence nor quality have been verified by WHO.

Recommended action

1. Consult with the national drug regulatory authority to establish the best course of action.

2. Prepare and implement a communication strategy addressed to prescribers and patients.

3. Take the necessary measures to switch to alternative prequalified products listed on the WHO Prequalification website (5). In this regard, the following actions are recommended in specific situations:

(a) The procurement of the withdrawn drugs is considered, but they have not yet been ordered. Withdrawn products should not be ordered. Instead, other prequalified products should be ordered until the withdrawn medicines are reinstated on WHO's list of prequalified products.

(b) Withdrawn drugs have been ordered to continue or scale up treatment programmes. Withdrawn drugs that have been ordered, but not received, should not be accepted. In this case, alternative prequalified products should be ordered instead. However, if alternative suppliers are not immediately available and the non-

acceptance of the ordered products could lead to an inability to continue or to start treating patients, the risk of withholding treatment is higher than that of providing medicines whose bioequivalence is not proven but which have, otherwise, been prequalified. In this case it would be justified to accept and use the withdrawn products. For follow-up orders, only prequalified products should be used.

Next steps

WHO has already received plans from manufacturers indicating proposed dates for submission of new study reports and WHO will carry out data assessment and site inspections as required.

WHO is in the process of inspecting other CROs which have conducted bioequivalence studies for products. For new applications, WHO has introduced inspections of CROs and laboratories for compliance with GCP and GLP as prerequisites for prequalification.

WHO has also initiated a programme of inspections of manufacturers of active pharmaceutical ingredients (APIs) including APIs used in anti-malaria and antituberculosis products, and this will be extended with an initial focus on antiretrovirals.

References

1. Prequalification of HIV drugs. *WHO Drug Information*, 17(3): 160 (2003).
2. WHO Press Release, WHO 79, 13 July 2004.
3. WHO Press Release, WHO 87. 30 November 2004.
4. The important world of drug prequalification. *The Lancet*, 364, No 9448, 20 November 2004.
5. WHO Prequalification Project website at: <http://mednet3.who.int/prequel/>

Combining TB and HIV treatment to save lives

Expanding access to tuberculosis treatment, combined with introducing HIV testing and antiretroviral (ARV) delivery into TB programmes, could save the lives of as many as 500 000 Africans living with HIV every year and is one of the most cost-effective ways to ensure the survival of HIV-positive people. Joint TB and HIV interventions are among the best ways to accelerate access to ARVs and to help reach WHO's 3 by 5 target of three million people on HIV treatment by the end of 2005.

Of the estimated 25 million Africans now living with HIV, about eight million also harbour the bacillus that causes TB. Each year, 5–10% of these eight million co-infected people develop active TB and up to half, or four million, will develop the disease at some point in their lives. Without TB treatment, HIV infected people with TB typically die within months. Yet national TB programmes in Africa are currently treating fewer than half of HIV-positive people with active TB — despite the fact that they respond just as well to TB treatment as HIV-negative people, and the cost of a TB drug regimen can be as low as US\$ 10 per patient. But few TB patients are currently offered an HIV test, and only a handful receive ARVs. Providing ARVs to HIV infected TB patients is now a WHO standard of care policy.

Reference: WHO press release 21 September 2004. on <http://www.who.int/>

Recent Publications and Sources of Information

Three new quality assurance guidelines endorsed by WHO Expert Committee

The work of the Expert Committee on Specifications for Pharmaceutical Preparations has a direct impact on a number of WHO priorities and policy objectives related to quality assurance, including the 3 by 5 Strategy, access to essential medicines for HIV/AIDS, tuberculosis and malaria, development of international standards for essential medicines, and the TRIPS agreement.

During its latest meeting in Geneva from 25 to 29 October 2004, the Expert Committee reviewed recent progress and some 62 working documents, including 12 new or revised general guidance texts. These cover regulatory guidance on interchangeability of medicines, fixed-dose combinations and their regulation, new guidance on good manufacturing practices (GMP) sampling procedures and stability testing. Three guidelines were adopted:

- The WHO GMP text on water for pharmaceutical use.
- WHO Guidelines on sampling of pharmaceuticals and related materials.
- Guidelines for registration of fixed-dose combination medicinal products.

In addition, discussion took place concerning new monographs to be included in *The International Pharmacopoeia* on antiretrovirals, fixed-dose combinations for tuberculosis, and antimalarials. A number of recommendations were also made, including the possibility of holding more frequent meetings in order to offer advice in a more timely manner.

The work of the Committee also includes development of internationally validated specifications and international chemical reference substances for medicines still under patent in many parts of the world. The Committee also serves as the scientific advisory body on the provision of guidance texts for the WHO Prequalification

Programme for medicines for HIV/AIDS, TB and malaria.

Reference: http://www.who.int/medicines/organization/qsm/expert_committee/expertcomm.shtml

WHO Medicines Bookshelf

The latest version of the WHO Medicines Bookshelf CD-ROM contains over 350 medicines-related publications, in English, French and Spanish, taken primarily from materials published by the Department of Essential Drugs and Medicines Policy (EDM). The Bookshelf covers:

- access to essential medicines
- rational use of medicines
- national drug policy
- quality and safety issues
- traditional medicine.

Core publications from other sources are also included on the CD-ROM, with the kind permission of the organizations concerned.

For those in areas where Internet access is particularly slow or unavailable, the Bookshelf also serves as a self-contained medicines information resource. For this reason, a version of the Essential Medicines Library (totalling 20 MB) has been included on the CD-ROM. The Library includes the WHO Model Formulary, and the interface serves as a seamless gateway to a wide range of useful web sites.

WHO Medicines Bookshelf is available free of charge from the EDM Documentation Centre, World Health Organization, 1211 Geneva 27, Switzerland or by e-mail: edmdoccentre@who.int

International Conference on Improving Use of Medicines

The goal of improving global access to medicines cannot be fulfilled without a corresponding improvement in use. This is a key message from the second International Conference on Improving Use of Medicines (ICIUM 2004), held 30 March – 2 April in Chiang Mai, Thailand. Four hundred and

seventy-two public health researchers and policy makers from 70 countries met to discuss research and interventions to improve the use of medicines in resource-limited settings.

Conference materials from ICIUM 2004 are now available on <http://www.icium.org> and include abstracts and slides from posters and presentations, selected videos and a summary of the conference recommendations.

The conference spanned themes on international and national policy making, hospitals and prescribing, health professionals, retail pharmaceutical sellers, and consumers. Discussion within each theme centred on specific health topics, including access to medicines, HIV/AIDS, malaria, tuberculosis, adult illness, children's health, and antimicrobial resistance.

The conference highlighted the need to move from small-scale research projects to implementing large-scale programmes that achieve public health impact. Many promising and successful interventions were presented at ICIUM. However, there are few reports of effective national efforts to improve the use of medicines on a large scale and in a sustainable manner. Thus a major research challenge is to achieve large-scale and sustained improvements within health systems. Evidence presented made it clear that misuse of medicines continues to be widespread and has serious health and economic implications, especially in resource-poor settings. However, effective solutions for some serious medicines problems already exist. Participants called upon governments to implement policies and programmes in the priority areas of implementing national medicines programmes to improve medicines use and scaling up interventions to national level in a sustainable way.

In addition to these key policy recommendations, consensus recommendations concerning policy implementation and priority research have been organized under 25 individual topic headings at the ICIUM website. These recommendations summarize what is known about improving the use of medicines in non-industrialized settings. It is hoped that they will be widely promulgated among policymakers and form the basis for applied research programmes on medicines use in the coming years.

Reference: <http://www.icium.org>

International network on HIV/AIDS for pharmacists

The newly launched International Network for Pharmacists on HIV/AIDS is an initiative created by the International Pharmaceutical Federation (FIP).

The Network aims to provide a platform for discussion and information sharing among pharmacists interested in HIV/AIDS.

Documentation available on the site includes:

- A literature review on the effectiveness and cost-effectiveness of pharmacist interventions in improving the prevention and treatment of HIV/AIDS;
- The HIV/AIDS training modules, prepared on behalf of FIP, are now being reviewed by WHO for endorsement,

There are also various links to related tools and material. Comments on this new network, and the training and review documents are welcomed and can be sent to hiv aids@fip.org.

Reference: <http://www.fip.org/hiv aids>.

Managing pharmaceuticals internationally

The availability of essential drugs is a key determinant of public health in many countries and addressing the inequalities in drug supply is a major challenge. *Managing Pharmaceuticals in International Health* aims to provide an introduction to international pharmaceutical policy, the key players and their roles. It discusses achievements, what remains to be done and prospects for the future.

The book should be of interest to all those who wish to learn more about an important area of international health, those involved with the management of medicines at any level, and with an interest in improving access to medicines for all in a fair and equitable way.

Reference: *Managing Pharmaceuticals in International Health* ISBN 3-7643-6601-X available from info@birkhauser.ch or <http://www.birkhauser.ch>

New brochure on adverse reaction reporting

Health Canada has developed a new brochure on adverse reaction reporting by health care professionals and consumers. The brochure covers what and when to report, how to submit a report, and how to access safety information on marketed health products on the Internet by subscribing to Health Canada's *Health_Prod_Info* mailing list.

Reference: http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/ar_reporting_brochure_e.pdf.

International chemical reference substances for malaria

Many developing countries are facing a growing problem of substandard and counterfeit medicines entering their markets. To enable governments to confront this issue by testing the quality of essential medicines, WHO has established a collection of international chemical reference substances (ICRS). To date, about 220 ICRS and 70 international reference spectra are available.

ICRS are established upon the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. New reference substances have been released for artemisinin derivatives included in the WHO Model List of Essential Medicines. Preparation of new international reference standards for antiretrovirals is under way. The ICRS are based on specifications and principles published in *The International Pharmacopoeia*. Using the ICRS, national authorities, manufacturers and other third parties involved in quality control testing can set up secondary and working standards. The ICRS have been tested for all analytical parameters in addition to comparative standards. A Certificate of Analysis is provided with the ICRS.

The price of these substances is lower than from commercial sources, making the ICRS particularly attractive for purchase by developing countries. The WHO Collaborating Centre for Chemical Reference Substances is based at the Swedish Apoteket AB and is responsible for the establishment, storage and worldwide distribution of the ICRS. This involves obtaining suitable candidate material, usually from pharmaceutical companies, characterization of purity and suitability through analytical examination, storage of the adopted ICRS and monitoring of stability.

Further information, catalogue and orders are available through the following links :

<http://www.who.int/medicines/organization/qsm/activities/qualityassurance/pharmacopea/i-pharmacop.html>

<http://www.who.int/medicines/organization/qsm/activities/qualityassurance/pharmacopea/i-pharmacop.html>

<http://www.apl.apoteket.se/Engelska/who/index.htm?index2.htm~vy>

<http://www.apl.apoteket.se/Engelska/who/index.htm?index2.htm~vy>

New physician guidelines on commercial relationships

The World Medical Association (WMA) has issued guidelines for physicians on how to handle relationships with the commercial sector, such as gifts, conference attendance, research and affiliations. The move is aimed to improve transparency of relationships with industry. Although it is acknowledged that industry support may help doctors carry out research and learn about new medical developments, conflicts of interest could occur if commercial considerations affect a doctor's objectivity. The guidelines set out the following principles involving sponsored attendance at medical conferences.

- The main purpose of the conference must be the exchange of professional or scientific information.
- Hospitality during the conference should be of secondary importance.
- The name of the financial sponsor should be publicly disclosed.
- Presentation of material must be scientifically accurate, give a balanced view of possible treatment options and not be influenced by the sponsoring organization.

With regard to acceptance of gifts, these should not be accepted unless allowed by law or other relevant policy of the national medical association. They should be of a nominal value — not in cash, and not dependant on use of certain medicines, material or instruments or depend on referral of patients to a certain facility.

Any sponsored research should be disclosed at the time of publication of the results, and doctors should be free to publish unfavourable results. Affiliations should not compromise integrity or conflict with obligations to patients.

References

1. WMA sets rules on how doctors handle industry sponsorship. *British Medical Journal*, **329**: 876 (2004).
2. World Medical Association, <http://www.wma.net>

COHRED and Research into Action

The Council on Health Research for Development (COHRED) is an international nongovernmental organization working towards enabling countries to set up and use health research to foster health, equity in health, and development.

A special edition of the COHRED newsletter, *Research into Action*, has been issued. It looks at COHRED's impact on health research for development since it was established in 1993. Following this review, COHRED's new strategic direction, activities and vision for the future are presented.

Research into Action, at http://www.cohred.ch/documents_COHREDweb/Newsletters/SpecialEdition.pdf and UNDP/WorldBank/WHO-TDR at <http://www.who.int/tdr/topmenu/news/>

New antimicrobial resistance website for the public

The United Kingdom National Electronic Library of Infection (NELI) has set up an antimicrobial resistance website at <http://www.antibioticresistance.org.uk> The site has been developed in response to current concerns about antimicrobial resistance and provides information for the public to promote appropriate use of antimicrobials.

Featured resources include:

- Learn About Antimicrobial Resistance. What are microbes and what is antimicrobial resistance? How do we become ill and how does our immune system work?
- Antimicrobial Resistance & Common Illnesses. How should antimicrobials be used to treat common illnesses? Why don't we always need to take them?

- Preventing Antimicrobial Resistance' How can we help prevent antimicrobial resistance? Do anti- bacterials cause resistance? What about the use of antimicrobials in farming or protecting against the effects of bio- terrorism?

- News on current articles, related resources and

Reference: <http://www.antibioticresistance.org.uk/>

Evaluation of medicinal products in children

An increase in the number of studies performed in children is expected as a consequence of the new European regulation on medicinal products in children. The actors of drug evaluation in children should be prepared for this, and a teaching programme has been organized during February and March 2005 in Brussels, Belgium, by the European Society for Developmental Perinatal and Paediatric Pharmacology.

Objectives of the course cover paediatric pharmacology, drug development and use, clinical trials and postmarketing surveillance, and drug evaluation in children.

Reference: sec_esdp_eudipharm@hotmail.com

Procurement of medicines in HIV

The World Bank's Implementation Acceleration Team was created to improve inadequate procedures and practices for a faster and more flexible intervention. *A Decision Maker's Guide to the Procurement of Medicines and Related Supplies*, represents an important step in dealing with HIV/AIDS, and particularly the purchase of antiretrovirals. The Guide has been developed for implementing agencies and donors and sets out principles and guidance to ensure that procurement will fit within overall well/functioning supply management system.

Battling HIV/AIDS. A Decision Maker's Guide to the Procurement of Medicines and Related Supplies. The World Bank. ISBN 0-8213-5848-0

Therapeutic guidelines: dermatology

The Therapeutic Guidelines are written for prescribers and other health professionals. They are independent, peer reviewed, regularly

updated and provide independent, practical and succinct therapeutic information. All Therapeutic Guideline titles are endorsed by the Royal Australian College of General Practitioners, the National Prescribing Service, and the International Society of Drug Bulletins.

This current title is also endorsed by Australasian College of Dermatologists as well as the Australian College of Rural and Remote Medicine, the Royal Australian College of Physicians, the Royal College of Nursing, Australia and the Society of Hospital pharmacists of Australia.

Therapeutic Guidelines: Dermatology. Version 2. August 2004. ISSN 1440-6357. Sample sections are available the Therapeutic Guidelines website at <http://www.tg.com.au>

International Pharmacopoeia available on CD-ROM

The International Pharmacopoeia comprises a collection of recommended procedures for analysis and specifications for the determination of pharmaceutical substances, excipients, and dosage forms that are intended to serve as source material for reference or adaptation and to establish pharmacopoeial requirements.

The collection of Volumes 1 to 5 have now been grouped on a single CD-ROM.

Available free of charge from the EDM Documentation Centre, World Health Organization, 1211 Geneva 27, Switzerland or by e-mail: edmdoccentre@who.int

Safety monitoring of herbal medicines

Many people in the world take herbal medicines for their health care and safety is a fundamental principle in the provision of herbal products. The *WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems* identify particular challenges posed in monitoring the safety of herbal medicines effectively and propose approaches for addressing them. Special attention is also given to reporting adverse reactions to herbal medicines, and to the analysis of the causes of adverse reactions.

Objectives of the guidelines are to:

- Strengthen national pharmacovigilance capacity and enhance effective safety monitoring,
- Provide technical guidance on pharmacovigilance and inclusion of herbal medicines.
- Provide standard definition of terms.
- Promote and strengthen information exchange internationally.

The guidelines were developed to enhance and broaden safety monitoring to encompass herbal medicines. It is not the intention of the guidelines to suggest that a separate system should be instituted for herbal medicines.

Currently, the majority of adverse events related to the use of herbal products and herbal medicines that are reported are attributable either to poor product quality or to improper use. Countries are encouraged to strengthen national regulation, registration and quality assurance and control, as well as to give greater attention to consumer education and to qualified practice in the provision of herbal medicines.

WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems, 2004, ISBN 92 4 159221 4. World Health Organization, 1211 Geneva 27, Switzerland or by e-mail: edmdoccentre@who.int

Medicinal plant guidelines translated

The *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants* are an important initial step to ensuring provision of good quality, safe herbal medicines and ecologically sound cultivation practices for future generations. The Guidelines cover the spectrum of cultivation and collection activities, including site selection, climate and soil considerations and identification of seeds and plants.

The guidelines have now been translated into all six official WHO languages and are available in Arabic, Chinese, English, French, Russian and Spanish.

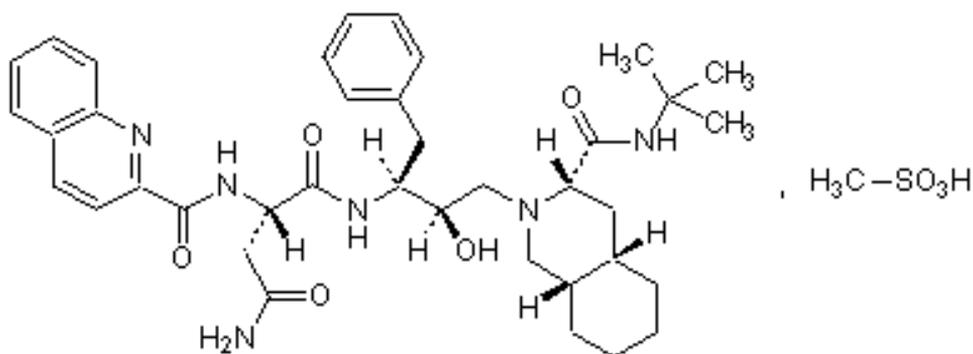
WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants. World Health Organization, 1211 Geneva 27, Switzerland or by e-mail: publications@who.int

Consultation Documents

The International Pharmacopoeia – monographs for antiretrovirals

Within the framework of the Procurement, Quality and Sourcing Project for HIV, Tuberculosis and Malaria (<http://www.who.int/prequal>), *The International Pharmacopoeia* is collaborating with manufacturers, independent analytical drug quality control laboratories, national and regional pharmacopoeial bodies, research, governments, and regulatory bodies to provide specifications and monographs for the following antiretroviral agents: abacavir, didanosine, efavirenz, indinavir, lamivudine, nelfinavir, nevirapine, ritonavir, saquinavir, stavudine, zidovudine. A draft monograph for saquinavir mesilate (below) is now being circulated for consultation. Please forward any comments to: Quality and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland or kopps@who.int.

Saquinaviri mesilas (1st draft) Saquinavir mesilate



$C_{38}H_{50}N_6O_5 \cdot CH_4O_3S$

Relative molecular mass. 767.0

Chemical name. (2*S*)-*N'*-[(1*S*,2*R*)-1-benzyl-3-[(3*S*,4*aS*,8*aS*)-3-[(1,1-dimethylethyl)carbamoyl]octahydroisoquinolin-2(1*H*)-yl]-2-hydroxypropyl]-2-[(quinolin-2-ylcarbonyl)amino]butanediamide methanesulfonate; CAS Reg. No. 149845-06-7.

Description. A white or almost white powder.

Solubility. Very slightly soluble in water and sparingly soluble in methanol.

Category. Antiretroviral (protease inhibitor).

Storage. Saquinavir mesilate should be kept in a well-closed container, protected from light.

Additional information. Saquinavir mesilate is slightly hygroscopic.

REQUIREMENTS

Saquinavir mesilate contains not less than 98.5 % and not more than 101.0 % of $C_{38}H_{50}N_6O_5 \cdot CH_4O_3S$ calculated with reference to the dried substance.

Identity tests

Either tests A and B or test C may be applied.

A. Choice between two alternatives A.1. (UV detection) or A.2. (spraying reagent) *Note:* UV detection is preferred due to its higher sensitivity.

A.1. Carry out the test as described under "Thin-layer chromatography" (Vol. 1, p. 83*), using silica gel R6 as the coating substance and a mixture of 8 volumes of dichloromethane R and 2 volumes of 2-propanol R as the mobile phase. Apply separately to the plate 5 ml of each of the following 2 solutions in methanol (A) 1 mg of Saquinavir mesilate per ml and (B) 1 mg of saquinavir mesilate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or with a hair-dryer with cold air. Examine the chromatogram in ultraviolet light (254 nm).

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

A.2. Carry out the test as described under "Thin-layer chromatography" (Vol. 1, p. 83*), using silica gel R5 as the coating substance and a mixture of 8 volumes of dichloromethane R and 2 volumes of 2-propanol R as the mobile phase as the mobile phase. Apply separately to the plate 5 ml of each of the following 2 solutions in methanol (A) 1 mg of saquinavir mesilate per ml and (B) 1 mg of saquinavir mesilate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or with a hair-dryer with cold air. Dip the plate in dilute basic potassium permanganate (1 g/l) TS. Examine the chromatogram in daylight.

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

B. The absorption spectrum of a 10 µg/ml solution in methanol R, when observed between 220 nm and 280 nm, exhibits one maximum at about 239 nm; the specific absorbance ($A_{1\text{cm}}^{1\%}$) calculated with reference to the dried substance is 570 to 630.

[Note from Secretariat: Would it be possible to check the specific absorbance range? Another possibility would be to replace test B by the melting point range (233–234 °C). Please comment.]

C. Carry out the examination as described under "Spectrophotometry in the infrared region" (Vol. 1, p. 40*). The infrared absorption spectrum is concordant with the spectrum obtained from saquinavir mesilate RS or with the *reference spectrum* of saquinavir mesilate.

Specific optical rotation. Use a 5.0 mg/ml solution in methanol R and calculate with reference to the dried substance; $[\alpha]_D^{20} = -33^\circ$ to -39° .

Heavy metals. Use 0.5 g in 30 ml of methanol R for the preparation of the test solution as described under "Limit test for heavy metals", Procedure 2, (Vol. 1, p. 118*); determine the heavy metals 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 5 hours at 105 °C; it loses not more than 10 mg/g.

Related substances. 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 base-deactivated octadecylsilyl silica gel for chromatography R (5 µm).

* Refers to *The International Pharmacopoeia*

Use the following conditions for gradient elution:

Mobile phase A: 50 volumes of a mixture of 5 parts of acetonitrile R and 2 parts methanol R, 15 volumes of phosphate buffer pH 3.4 and 35 volumes of purified water.

Mobile phase B: 70 volumes of acetonitrile R, 15 volumes of phosphate buffer pH 3.4 and 15 volumes of purified water.

Prepare the phosphate buffer pH 3.4 by dissolving 4.88 g of anhydrous sodium dihydrogen phosphate in 800 ml of purified water, adjust the pH to 3.4 by adding phosphoric acid (105 g/l) and dilute to 1000 ml with purified water.

Time (min)	Mobile phase A (%)	Mobile phase B (%)	Comments
0–25	100	0	Isocratic
25–45	100 to 45	0 to 55	Linear gradient
45–55	45	55	Isocratic
55–60	45 to 100	55 to 0	Linear gradient
60–70	100	0	Isocratic re-equilibration

Prepare the following solutions using mobile phase A as diluent. For solution (1) use 0.5 mg of saquinavir mesilate per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 0.5 µg of per ml.

For the system suitability test: prepare solution (3) using 2 ml of solution (1) and 5 ml of sulfuric acid (475 g/l), heat carefully in a boiling water-bath for 30 minutes.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 220 nm.

Maintain the column temperature at 30 °C.

Inject 20 µl of solution (3). The test is not valid unless the resolution between the peak due to saquinavir and the peak of similar size with a retention time of about 0.45 relative to the saquinavir peak is not less than 14. The test is also not valid unless the resolution between two smaller peaks of similar size, eluted after the saquinavir peak and which increase during decomposition, is not less than 4.0. The ratio of the retention times of these two peaks relative to the saquinavir peak is about 1.8 and 1.9 respectively. If necessary adjust the amount of acetonitrile in both mobile phases A and B, or adjust the gradient programme.

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

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). In the chromatograms obtained with solution (1), the area of any peak, other than the principal peak, is not greater than that obtained with solution (2) (0.1 %). The sum of the areas of all peaks, other than the principal peak, is not greater than five times the area of the principal peak obtained with solution (2) (0.5 %). Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05 %).

Assay. Dissolve about 0.500 g, accurately weighed, in 70 ml of methanol R and titrate with sodium hydroxide (0.1 mol/l) VS determining the end point potentiometrically. Perform a blank determination and make the necessary correction. Each ml of sodium hydroxide (0.1 mol/l) VS is equivalent to 76.70 mg of $C_{38}H_{50}N_6O_5 \cdot CH_4O_3S$; calculate with reference to the dried substance.

* Refers to *The International Pharmacopoeia*

Reagent

Silica gel for chromatography, octadecylsilyl, base deactivated

A very finely divided silica gel, pre-treated before the bonding of octadecylsilyl groups to minimize the interaction with basic compounds.

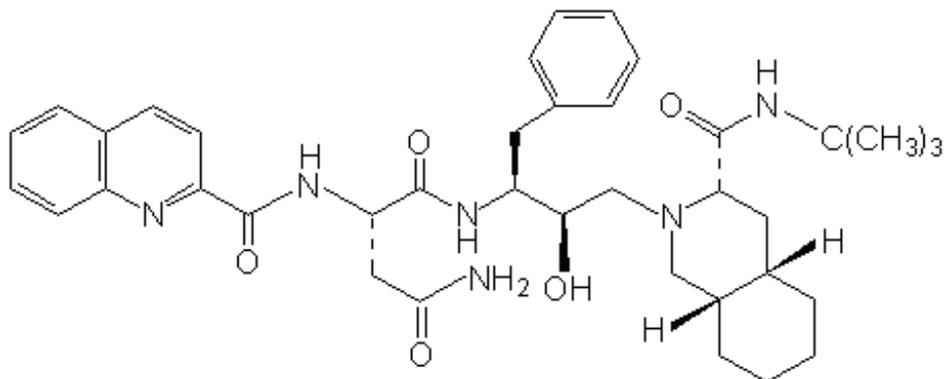
Potassium permanganate, basic, dilute (1 g/l) TS

A solution of potassium permanganate R containing about 1 g of KMnO_4 per litre of sodium hydroxide (1 mol/l).

The International Pharmacopoeia: monographs for antiretrovirals

Within the framework of the Procurement, Quality and Sourcing Project for HIV, Tuberculosis and Malaria (<http://www.who.int/prequal>), *The International Pharmacopoeia* is collaborating with manufacturers, independent analytical drug quality control laboratories, national and regional pharmacopoeial bodies, research, governments, and regulatory bodies to provide specifications and monographs for the following antiretroviral agents: abacavir, didanosine, efavirenz, indinavir, lamivudine, nelfinavir, nevirapine, ritonavir, saquinavir, stavudine, zidovudine. A draft monograph for saquinavir (below) is now being circulated for consultation. Please forward any comments to: Quality and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland or kopps@who.int.

Saquinavirum (1st draft) Saquinavir



Relative molecular mass. 670.8

Chemical name. (*S*)-*N*[(*S*)-*N*-(1-*R*)-2-[(1-*R*)-2-{3*S*,4*aS*,8*aS*}-3-(*tert*-butylcarbamoyl) octahydro-2(1*H*)-isoquinolyl]-1-hydroxyethyl]phenethyl]-2-quinaldamido succinamide; CAS Reg. NO.12777-20-8.

Description. A white or almost white powder.

Solubility. Practically insoluble in water and soluble in methanol.

Category. Antiretroviral (protease inhibitor).

* Refers to *The International Pharmacopoeia*

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

Additional information. Saquinavir is slightly hygroscopic.

REQUIREMENTS

Saquinavir contains not less than 98.5 % and not more than 101.0 % of $C_{38}H_{50}N_6O_5$, calculated with reference to the dried substance.

Identity tests

Either tests A and B or test C may be applied

A. Choice between two alternatives A.1. (UV detection) or A.2. (spraying reagent). *Note:* UV detection is preferred due to its higher sensitivity.

A.1. Carry out the test as described under "Thin-layer chromatography" (Vol. 1, p. 83*), using silica gel R6 as the coating substance and a mixture of 8 volumes of dichloromethane R and 2 volumes of 2-propanol R as the mobile phase. Apply separately to the plate 5 ml of each of the following 2 solutions in methanol (A) 1 mg of saquinavir per ml and (B) 1 mg of saquinavir RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or with a hair-dryer with cold air. Examine the chromatogram in ultraviolet light (254 nm).

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

A.2. Carry out the test as described under "Thin-layer chromatography" (Vol. 1, p. 83*), using silica gel R5 as the coating substance and a mixture of 8 volumes of dichloromethane R and 2 volumes of 2-propanol R as the mobile phase as the mobile phase. Apply separately to the plate 5 ml of each of the following 2 solutions in methanol (A) 1 mg of saquinavir per ml and (B) 1 mg of saquinavir RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or with a hair-dryer with cold air. Dip the plate in dilute basic potassium permanganate (1 g/l) TS. Examine the chromatogram in daylight.

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

B. The absorption spectrum of a 20 µg/ml solution in methanol R, when observed between 220 nm and 280 nm, exhibits one maximum at about 238 nm; the specific absorbance ($A_{1\text{cm}}^{1\%}$) calculated with reference to the dried substance is 335 to 365.

[Note from Secretariat: Would it be possible to check the specific absorbance range? Another possibility would be to replace test B by the melting point range (151–152°C). Please comment].

C. Carry out the examination as described under "Spectrophotometry in the infrared region" (Vol. 1, p. 40*). The infrared absorption spectrum is concordant with the spectrum obtained from saquinavir RS or with the *reference spectrum* of saquinavir.

Specific optical rotation. Use a 5.0 mg/ml solution in methanol R; $[\alpha]_D^{20} = -20^\circ$ to -24° .

Heavy metals. Use 1.0 g in 30 ml of methanol R for the preparation of the test solution as described under "Limit test for heavy metals", Procedure 2, (Vol. 1, p. 118*); determine the heavy metals content according to Method A (Vol. 1, p. 119*); not more than 10 µg/g.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry for 5 hours at 105 °C; it loses not more than 20 mg/g.

* Refers to *The International Pharmacopoeia*

Related substances. 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 base-deactivated octadecylsilyl silica gel for chromatography R (5 µm).

Use the following conditions for gradient elution:

Mobile phase A: 50 volumes of a mixture of 5 parts of acetonitrile R and 2 parts methanol R, 15 volumes of phosphate buffer pH 3.4 and 35 volumes of purified water.

Mobile phase B: 70 volumes of acetonitrile R, 15 volumes of phosphate buffer pH 3.4 and 15 volumes of purified water.

Prepare the phosphate buffer pH 3.4 by dissolving 4.88 g of anhydrous sodium dihydrogen phosphate in 800 ml of purified water, adjust the pH to 3.4 by adding phosphoric acid (105 g/l) and dilute to 1000 ml with purified water.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–25	100	0	Isocratic
25–45	100 to 45	0 to 55	Linear gradient
45–55	45	55	Isocratic
55–60	45 to 100	55 to 0	Linear gradient
60–70	100	0	Isocratic re-equilibration

Prepare the following solutions using mobile phase A as diluent. For solution (1) use 0.5 mg of saquinavir per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 0.5 µg of saquinavir per ml.

For the system suitability test: prepare solution (3) using 2 ml of solution (1) and 5 ml of sulfuric acid (475 g/l), heat carefully in a boiling water-bath for 30 minutes.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 220 nm.

Maintain the column temperature at 30 °C.

Inject 20 µl of solution (3). The test is not valid unless the resolution between the peak due to saquinavir and the peak of similar size with a retention time of about 0.45 relative to the saquinavir peak is not less than 14. The test is also not valid unless the resolution between two smaller peaks of similar size, eluted after the saquinavir peak and which increase during decomposition, is not less than 4.0. The ratio of the retention times of these two peaks relative to the saquinavir peak is about 1.8 and 1.9 respectively. If necessary adjust the amount of acetonitrile in both mobile phases A and B, or adjust the gradient program.

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

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). In the chromatograms obtained with solution (1), the area of any peak, other than the principal peak, is not greater than that obtained with solution (2) (0.1 %). The sum of the areas of all peaks, other than the principal peak, is not greater than five times the area of the principal peak obtained with solution (2) (0.5 %). Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Assay. Dissolve 0.300 g, accurately weighed, in 50 ml of glacial acetic acid R1 and titrate with perchloric acid (0.1 mol/l) VS, determine the end point potentiometrically as described under “Non aqueous

* Refers to *The International Pharmacopoeia*

titration" method A (Vol.1, p. 131*). Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 33.54 mg of $C_{38}H_{50}N_6O_5$; calculate with reference to the dried substance.

Reagent

Silica gel for chromatography, octadecylsilyl, base deactivated

A very finely divided silica gel, pre-treated before the bonding of octadecylsilyl groups to minimize the interaction with basic compounds.

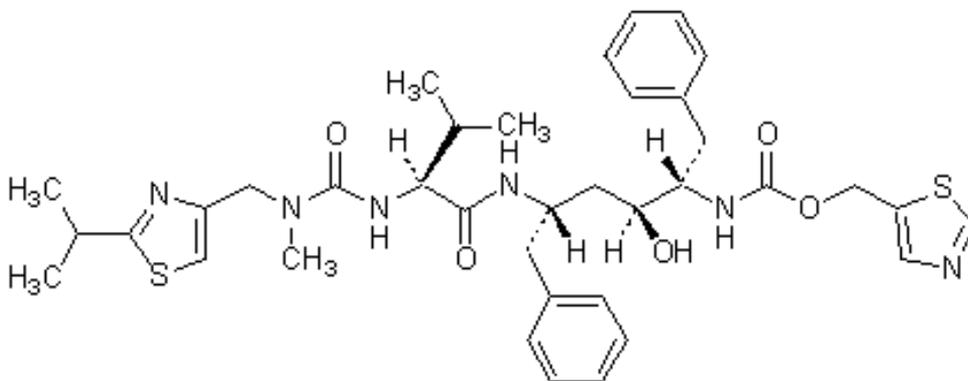
Potassium permanganate, basic, dilute (1 g/l) TS

A solution of potassium permanganate R containing about 1 g of $KMnO_4$ per litre of sodium hydroxide (1 mol/l).

The International Pharmacopoeia: monographs for antiretrovirals

Ritonavirum (1 st draft) Ritonavir

Within the framework of the Procurement, Quality and Sourcing Project for HIV, Tuberculosis and Malaria (<http://www.who.int/prequal>), *The International Pharmacopoeia* is collaborating with manufacturers, independent analytical drug quality control laboratories, national and regional pharmacopoeial bodies, research, governments, and regulatory bodies to provide specifications and monographs for the following antiretroviral agents: abacavir, didanosine, efavirenz, indinavir, lamivudine, nelfinavir, nevirapine, ritonavir, saquinavir, stavudine, zidovudine. A draft monograph for ritonavir (below) is now being circulated for consultation. Please forward any comments to: Quality and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland or kopps@who.int.



$C_{37}H_{48}N_6O_5S_2$

Relative molecular mass. 721.0

Chemical name. thiazol-5-ylmethyl [(1*S*,2*S*,4*S*)-1-benzyl-2-hydroxy-4-[[2*S*]-3-methyl-2-[[methyl][2-(1-methylethyl)thiazol-4-yl]methyl]carbamoyl]amino]butanoyl]amino]-5-phenylpentyl]carbamate; CAS Reg. NO.155213-67-5.

Description. A white or almost white powder.

* Refers to *The International Pharmacopoeia*

Solubility. Practically insoluble in water, freely soluble in methanol R, sparingly soluble in acetone R and very slightly soluble in acetonitrile R.

Category. Antiretroviral (protease inhibitor).

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

REQUIREMENTS

Ritonavir contains not less than 98.5 % and not more than 101.0 % of $C_{37}H_{48}N_6O_5S_2$, calculated with reference to the dried substance.

Identity tests (*Either tests A and B or test C may be applied.*)

A. TLC: to be added.

B. The absorption spectrum of a 40 µg/ml solution in methanol R, when observed between 220 nm and 280 nm, exhibits one maximum at about 240 nm; the specific absorbance ($A_{1\text{cm}}^{1\%}$) calculated with reference to the dried substance is 116 to 128.

C. Carry out the examination as described under "Spectrophotometry in the infrared region" (Vol. 1, p. 40*). The infrared absorption spectrum is concordant with the spectrum obtained from ritonavir RS or with the *reference spectrum* of ritonavir.

Specific optical rotation. Use a 20.0 mg/ml solution in methanol R; $[\alpha]_D^{20} = +7^\circ$ to $+10.5^\circ$.

Heavy metals. Use 1.0 g in 30 ml of methanol R for the preparation of the test solution as described under "Limit test for heavy metals", Procedure 2, (Vol. 1, p. 118*); determine the heavy metals 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 2 hours at 105 °C; it loses not more than 5 mg/g.

Related substances. 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 base-deactivated octadecylsilyl silica gel for chromatography R (5 µm).

Use the following conditions for gradient elution:

Mobile phase A: 35 volumes of acetonitrile R, 28 volumes sodium phosphate buffer pH 4.0 and 37 volumes of purified water.

Mobile phase B: 70 volumes of acetonitrile R, 28 volumes sodium phosphate buffer pH 4.0 and 2 volumes of purified water.

Prepare the sodium phosphate buffer pH 4.0 by dissolving 7.8 g of sodium dihydrogen phosphate dihydrate and 1.88 g of sodium hexanesulfonate R in 800 ml of purified water, adjust the pH to 4.0 by adding phosphoric acid (105 g/l) and dilute to 1000 ml with purified water.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–20	70	30	Isocratic
20–30	70 to 0	30 to 100	Linear gradient
30–40	0	100	Isocratic
40–45	0 to 70	100 to 30	Linear gradient
45–50	70	30	Isocratic re-equilibration

* Refers to *The International Pharmacopoeia*

Prepare the following solutions using mobile phase A as diluent. For solution (1) use 0.5 mg of ritonavir per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 0.5 µg of ritonavir per ml.

For the system suitability test: prepare solution (3) using 5 ml of solution (1) and 1 ml of sulfuric acid (475 g/l), heat in a boiling water bath for 20 minutes.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectro- photometer set at a wavelength of 240 nm.

Maintain the column temperature at 35° C.

Inject 20 µl of solution (3). The test is not valid unless the resolution between the principal peak and the peak with a retention time relative to the principal peak of about 0.8 is not less than 3.5. The test is also not valid unless the resolution between the principal peak and the peak with a retention time relative to the principal peak of about 1.5 is not less than 9.0. If necessary adjust the amount of acetonitrile in both mobile phases A and B, or adjust the gradient programme.

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

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). In the chromatograms obtained with solution (1), the area of any peak, other than the principal peak, is not greater than three times that obtained with solution (2) (0.3%). In the chromatograms obtained with solution (1), not more than two peaks, other than the principal peak, are greater than two times that obtained with solution (2) (0.2%). In the chromatograms obtained with solution (1), not more than four peaks, other than the principal peak, are greater than that obtained with solution (2) (0.1%). The sum of the areas of all peaks, other than the principal peak, is not greater than ten times the area of the principal peak obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Assay. Dissolve 0.250 g, accurately weighed, in 30 ml of glacial acetic acid R1 and titrate with perchloric acid (0.1 mol/l) VS, determine the end point potentiometrically as described under "Non aqueous titration" Method A (Vol. 1, p. 131*). Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 36.05 mg of $C_{37}H_{48}N_6O_5S_2$; calculate with reference to the dried substance.

Reagents

Silica gel for chromatography, octadecylsilyl, base deactivated

A very finely divided silica gel, pre-treated before the bonding of octadecylsilyl groups to minimize the interaction with basic compounds.

Sodium dihydrogen phosphate dihydrate

[Sodium biphosphate]; sodium phosphate, monobasic; $NaH_2PO_4 \cdot 2H_2O$

* Refers to *The International Pharmacopoeia*

The International Pharmacopoeia: monographs for tuberculosis medicines

Rifampicin, isoniazid and pyrazinamide tablets (1st draft)

Within the framework of the Procurement, Quality and Sourcing Project for HIV, Tuberculosis and Malaria (<http://www.who.int/prequal>), *The International Pharmacopoeia* is collaborating with manufacturers, independent analytical drug quality control laboratories, national and regional pharmacopoeial bodies, research, governments, and regulatory bodies to provide specifications and monographs for tuberculosis medicines. A draft monograph for Rifampicin, Isoniazid and pyrazinamide tablets (below) is now being circulated for consultation. Please forward any comments to: Quality and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland or kopps@who.int.

Category. Antituberculosis drugs.

Storage. Rifampicin, isoniazid and pyrazinamide tablets should be packaged in airtight containers, protected from light.

Additional information. Strengths in the current WHO Model List of Essential Medicines:

60 mg rifampicin, 30 mg isoniazid and 150 mg pyrazinamide.
150 mg rifampicin, 75 mg isoniazid and 400 mg pyrazinamide.
150 mg rifampicin, 150 mg isoniazid and 500 mg pyrazinamide.

REQUIREMENTS

Complies with the monograph for "Tablets" (see Vol. 4, p. 26*).

Rifampicin, isoniazid and pyrazinamide tablets contain not less than 90.0% and not more than 110.0% of the amounts of rifampicin ($C_{43}H_{58}N_4O_{12}$), isoniazid ($C_6H_7N_3O$) and pyrazinamide ($C_5H_5N_3O$) stated on the label.

Identity tests

Either test A and B or test C may be applied.

A. See the test described below under "Assay method A". The retention times of the isoniazid, and pyrazinamide peaks in the chromatogram of solution A correspond to those in the chromatogram of solution B.

B. See the test described below under "Assay method B". The retention time of the rifampicin peak in the chromatogram of solution A corresponds to that in the chromatogram of solution B.

C. Carry out the test as described under "Thin-layer chromatography" (Vol. 1, p. 83*), using silica gel R5 as the coating substance and a mixture of 100 volumes of methanol R and 1.5 volumes of strong ammonia solution R as the mobile phase. Apply separately to the plate 5 ml of each of the following two solutions in methanol R. For solution (A) shake a quantity of the powdered tablets equivalent to about 5 mg Isoniazid for 15 minutes with 5 ml of methanol R, filter, and use the filtrate. For solution (B) use 1 mg isoniazid RS and proportional quantities (according to the ratio in the tablet) of rifampicin RS and pyrazinamide RS per ml of methanol R. After removing the plate from the chromatographic chamber, allow it to dry in a current of air, place in a chamber with iodine vapours, and allow to stand for 20

* Refers to *The International Pharmacopoeia*

minutes. Examine the chromatogram immediately in daylight. The sensitivity can be improved by using silica gel R6 as the coating substance and examining the chromatogram in ultraviolet light (254 nm).

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

Related substances

Note: The limits for related substances are the maximum throughout the shelf-life of the finished pharmaceutical product.

Carry out the test as described under "High-performance liquid chromatography" (Vol. 5, p. 257*), using the conditions given below under Assay method B.

Inject alternately 10 µl each of solutions A and C.

In the chromatogram obtained with solution A the following peaks are eluted at the following retention ratio with reference to rifampicin (approximate retention time = 25 to 30 min.): rifampicin N-oxide = about 0.27; 3-(Isonicotinoylhydrazinomethyl)rifamycin = about 0.52; rifampicin quinone = about 0.70; 3-Formylrifamycin = about 0.87.

Measure the areas of the peak responses obtained in the chromatograms from solutions A and C, and calculate the content of the related substances as a percentage. In the chromatogram obtained with solution A, the area of the related substance peak corresponding to 3 (Isonicotinoylhydrazinomethyl) rifamycin is not greater than that obtained for the rifampicin peak with solution C (5.0%). No other peak is greater than half the area of the rifampicin peak obtained with solution C (2.5%). The sum of the areas of all the peaks, other than the principal peak, is not greater than twice the area of the rifampicin peak obtained with solution C (10.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution C. Disregard any peak with retention ratio less than 0.23 with reference to rifampicin.

[Note of Secretariat: The limits for the related substances must still be finalized.]

Assay

Tests A and B are applicable.

A. Determine by "High-performance liquid chromatography" (Vol. 5, p. 257*), using a stainless steel column (15 cm x 4.6 mm) packed with *stationary phase A* (5 µm (Luna® is suitable)). As the mobile phase, use a solution prepared as follows: dissolve 50 g ammonium acetate R in 1000 ml of water and adjust to pH 5.0 ± 0.05 with glacial acetic acid R. Mix 940 ml of this solution with 60 ml methanol R.

Prepare the following solutions in water. For solution (A) weigh and powder 20 tablets. Transfer a quantity of the powder equivalent to about 30 mg isoniazid, accurately weighed, to a 500 ml volumetric flask. Dissolve in about 400 ml water by shaking for about 15 minutes. Dilute to 500 ml with water. Filter a portion of this solution through a 0.45 µm filter, discarding the first few ml of the filtered solution. For solution (B) dissolve 30 mg isoniazid RS and a proportional quantity (according to the ratio in the tablet) of pyrazinamide RS in 500 ml water.

Operate with a flow rate of 2.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 240 nm.

Inject 20 µl of solution B. The test is not valid unless the resolution between the isoniazid and pyrazinamide peaks is not less than 2.

* Refers to The International Pharmacopoeia

Inject separately 20 µl of solution B in six replicate injections in the chromatographic system. The relative standard deviation of the peak areas of Isoniazid and Pyrazinamide, eluting in this order, is not more than 2.0%.

Inject alternately 20 µl each of solutions A and B.

Measure the areas of the peak responses obtained in the chromatograms from solutions A and B, and calculate the percentage content of Isoniazid (C₆H₇N₃O) and Pyrazinamide (C₅H₅N₃O).

B. Note: prepare fresh solutions and perform the tests without delay. Low-actinic glassware is recommended.

Determine by "High-performance liquid chromatography" (Vol. 5, p. 257*), using a stainless steel column (25 cm x 4.6 mm) packed with *stationary phase A* (5 µm)². As the mobile phase, use a mixture of 6 volumes of methanol R and 4 volumes of phosphate buffer pH 7.0 (potassium dihydrogen phosphate (0.01 mol/l), adjusted with sodium hydroxide (0.1 mol/l)).

Prepare the following solutions in methanol R. For solution (A) weigh and powder 20 tablets. Shake a quantity of the powder equivalent to about 0.15 g Rifampicin, accurately weighed, in 100 ml methanol R, filter and dilute 5 ml to 10 ml with methanol R. or solution (B) use 0.75 mg rifampicin RS per ml. For solution (C) dilute a suitable volume of solution A to obtain a concentration equivalent to 37.5 µg mg Rifampicin per ml. For the system suitability test prepare solution (D) containing 0.375 mg rifampicin RS per ml and 0.375 mg 3-formylrifampicin RS per ml.

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

Inject 10 µl of solution D. The test is not valid unless the resolution between the peaks is not less than 1.5.

Inject separately 10 µl of solution B in six replicate injections in the chromatographic system. The relative standard deviation of the peak area of Rifampicin is not more than 2.0%.

Inject alternately 10 µl each of solutions A and B.

Measure the areas of the peak responses obtained in the chromatograms from solutions A and B, and calculate the percentage content of Rifampicin (C₄₃H₅₈N₄O₁₂).

Dissolution test. To be added.

* Refers to *The International Pharmacopoeia*

The International Pharmacopoeia: monographs for tuberculosis medicines

Isoniazid and ethambutol hydrochloride tablets (1st draft)

Within the framework of the Procurement, Quality and Sourcing Project for HIV, Tuberculosis and Malaria (<http://www.who.int/prequal>), *The International Pharmacopoeia* is collaborating with manufacturers, independent analytical drug quality control laboratories, national and regional pharmacopoeial bodies, research, governments, and regulatory bodies to provide specifications and monographs for tuberculosis medicines. A draft monograph for Isoniazid and ethambutol hydrochloride tablets (below) is now being circulated for consultation. Please forward any comments to: Quality and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland or kopps@who.int.

Category. Antituberculosis drugs.

Storage. Should be protected from moisture.

Additional information. Strength in the current WHO Model List of Essential Medicines:

150 mg isoniazid
400 mg ethambutol hydrochloride.

REQUIREMENTS

Complies with the monograph for "Tablets" (see Vol. 4, p. 26*).

Isoniazid and ethambutol hydrochloride tablets contain not less than 90.0% and not more than 110.0% of the amounts of Isoniazid ($C_6H_7N_3O$) and Ethambutol hydrochloride ($C_{10}H_{24}N_2O_2 \cdot 2HCl$) stated on the label.

Identity tests

Either test A or test B may be applied.

A. See the test described below under "Assay". The retention times of the isoniazid and ethambutol hydrochloride peaks in the chromatogram of solution A correspond to those in the chromatogram of solution B.

B. Carry out the test as described under "Thin-layer chromatography" (Vol. 1, p. 83*), using silica gel R1 as the coating substance and a mixture of 100 volumes of methanol R and 1.5 volumes of strong ammonia solution R as the mobile phase. Apply separately to the plate 5 ml of each of the following two solutions in methanol R. For solution (A) shake a quantity of the powdered tablets equivalent to about 5 mg Isoniazid for 15 minutes with 5 ml of methanol R, filter, and use the filtrate. For solution (B) use 1 mg isoniazid RS and 2.67 mg ethambutol hydrochloride RS per ml of methanol R. After removing the plate from the chromatographic chamber, allow it to dry in a current of air, place in a chamber with iodine vapours, and allow to stand for 20 minutes. Examine the chromatogram immediately in daylight. The sensitivity can be improved by using silica gel R2 as the coating substance and examining the chromatogram in ultraviolet light (254 nm).

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

* Refers to *The International Pharmacopoeia*

Related substances

Tests A and B are applicable.

A. Aminobutanol. Carry out the test as described under "Thin-layer chromatography" (Vol. 1, p. 83), using silica gel R1 as the coating substance and a mixture of 55 volumes of ethyl acetate R, 35 volumes of glacial acetic acid R, 5 volumes of hydrochloric acid (~420g/l) TS, and 1 volume of water as the mobile phase. Apply separately to the plate 2 µl of each of the following 2 solutions in methanol R. For solution (A) shake a quantity of the powdered tablets equivalent to about 0.5 g of Ethambutol hydrochloride with 10 ml of methanol R for 5 minutes, filter, and use the filtrate. For solution (B) use 0.5 mg of aminobutanol R per ml of methanol R. After removing the plate from the chromatographic chamber, allow it to dry in air, heat at 105 °C for 5 minutes, cool, spray with triketohydrindene/cadmium TS, and heat again at 90 °C for 5 minutes. Examine the chromatogram in daylight.

Any spot corresponding to aminobutanol obtained with solution A is not more intense than that obtained with solution B.

B Isonicotinic acid. Carry out the test as described under "Thin-layer chromatography" (Vol. 1, p. 83), using silica gel R2 as the coating substance and a mixture of 5 volumes of ethyl acetate R, 2 volumes of acetone R, 2 volumes of methanol R, and 1 volume of water as the mobile phase. Apply separately to the plate 10 µl of each of the following 3 solutions. For solution (A) shake a quantity of the powdered tablets equivalent to about 0.1 g of Isoniazid with 10 ml of methanol R, filter, and use the filtrate. For solution (B) use 10 mg of isoniazid RS per ml of methanol R. For solution (C) dilute 1 volume of solution A to 100 volumes with methanol R. After removing the plate from the chromatographic chamber, allow to dry in air, and examine the chromatogram in ultraviolet light (254 nm).

Any spot obtained with solution A, other than the principal spot, is not more intense than that obtained with solution C. The relative R_f of isonicotinic acid is about 0.7 with reference to Isoniazid.

Assay

Determine by "High-performance liquid chromatography" (Vol. 5, p. 257*), using a stainless steel column (15 cm x 4.6 mm) packed with *stationary phase A* (5 µm) (Luna® is suitable). As the mobile phase, use a solution prepared as follows: dissolve 50 g ammonium acetate R and 0.2 g copper(II) acetate R in 1000 ml of water and adjust to pH 5.0 ± 0.05 with glacial acetic acid R. Mix 940 ml of this solution with 60 ml methanol R.

Prepare the following solutions in water. For solution (A) weigh and powder 20 tablets. Transfer a quantity of the powder equivalent to about 100 mg ethambutol hydrochloride, accurately weighed, to a 500 ml volumetric flask. Dissolve in about 400 ml water by shaking for about 15 minutes. Dilute to 500 ml with water. Filter a portion of this solution through a 0.45 µm filter, discarding the first few ml of the filtered solution. For solution (B) dissolve 100 mg ethambutol hydrochloride RS and 37.5 isoniazid RS in 500 ml water.

Operate with a flow rate of 2.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 270 nm.

Inject 20 µl of solution B. The test is not valid unless the resolution between the Isoniazid peak, with the shorter retention time, and the ethambutol hydrochloride peak is not less than 10.

Inject separately 20 µl of solution B in replicate injections in the chromatographic system. The relative standard deviation for peak areas of isoniazid and ethambutol hydrochloride in replicate injections of solution B is not more than 2.0%.

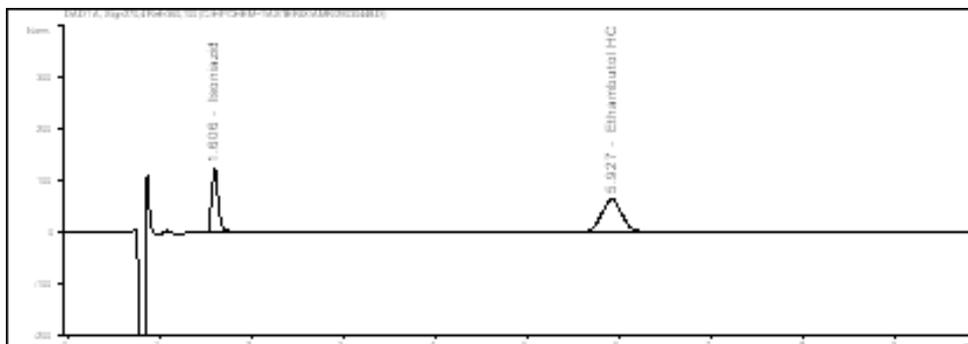
Inject alternately 20 µl each of solutions A and B.

Measure the areas of the peak responses obtained in the chromatograms from solutions A and B, and calculate the percentage of isoniazid (C₆H₇N₃O) and ethambutol hydrochloride (C₁₀H₂₄N₂O₂·2HCl).

* Refers to The International Pharmacopoeia

Dissolution test. To be added.

A typical chromatogram of Isoniazid and Ethambutol hydrochloride.



The International Pharmacopoeia: monographs for tuberculosis medicines

Rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride tablets (1st draft)

Within the framework of the Procurement, Quality and Sourcing Project for HIV, Tuberculosis and Malaria (<http://www.who.int/prequal>), *The International Pharmacopoeia* is collaborating with manufacturers, independent analytical drug quality control laboratories, national and regional pharmacopoeial bodies, research, governments, and regulatory bodies to provide specifications and monographs for tuberculosis medicines. A draft monograph for Rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride tablets (below) is now being circulated for consultation. Please forward any comments to: Quality and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland or kopps@who.int.

Category. Antituberculosis drugs.

Storage. Rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride tablets should be well protected from moisture and light.

Additional information. Strength in the current WHO Model List of Essential Medicines: 150 mg rifampicin, 75 mg isoniazid, 400 mg pyrazinamide and 275 mg ethambutol hydrochloride.

REQUIREMENTS

Complies with the monograph for "Tablets" (see Vol. 4, p. 26*).

Rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride tablets contain not less than 90.0% and not more than 110.0% of the amounts of rifampicin ($C_{43}H_{58}N_4O_{12}$), isoniazid ($C_6H_7N_3O$), pyrazinamide ($C_5H_5N_3O$) and ethambutol hydrochloride ($C_{10}H_{24}N_2O_2 \cdot 2HCl$) stated on the label.

Loss on drying. Dry freshly powdered tablets to constant mass under vacuum at 60 °C; it loses not more than 50 mg/g.

* Refers to *The International Pharmacopoeia*

Uniformity of content. Complies with the requirements of "Uniformity of contents for single-dose preparations" (Vol. 4, p. 46*) with respect to each active pharmaceutical ingredient.

Note: To be discussed in terms of The International Pharmacopoeia's general requirements for FDC tablets.

Identity tests

Either test A and B or test C may be applied.

A. See the test described below under "Assay method A". The retention times of the Isoniazid, Pyrazinamide and Ethambutol hydrochloride peaks in the chromatogram of solution A correspond to those in the chromatogram of solution B.

B. See the test described below under "Assay method B". The retention time of the rifampicin peak in the chromatogram of solution A corresponds to that in the chromatogram of solution B.

C. Carry out the test as described under "Thin-layer chromatography" (Vol. 1, p. 83*), using silica gel R1 as the coating substance and a mixture of 100 volumes of methanol R and 1.5 volumes of strong ammonia solution R as the mobile phase. Apply separately to the plate 5 ml of each of the following two solutions in methanol R. For solution (A) shake a quantity of the powdered tablets equivalent to about 5 mg Isoniazid for 15 minutes with 5 ml of methanol R, filter, and use the filtrate. For solution (B) use 2 mg rifampicin RS, 1 mg isoniazid RS, 5.33 mg pyrazinamide RS and 3.67 mg ethambutol hydrochloride RS per ml of methanol R. After removing the plate from the chromatographic chamber, allow it to dry in a current of air, place in a chamber with iodine vapours, and allow to stand for 20 minutes. Examine the chromatogram immediately in daylight. The sensitivity can be improved by using silica gel R2 as the coating substance and examining the chromatogram in ultraviolet light (254 nm).

The principal spots obtained with solution A correspond in position, appearance and intensity with those obtained with solution B. Rifampicin may exhibit a second spot with slightly lower R_f value, due to oxidation on the plate before development.

Related substances

Tests A and B are applicable.

A. **Aminobutanol.** Carry out the test as described under "Thin-layer chromatography" (Vol. 1, p. 83), using silica gel R1 as the coating substance and a mixture of 55 volumes of ethyl acetate R, 35 volumes of glacial acetic acid R, 5 volumes of hydrochloric acid (~420g/l) TS, and 1 volume of water as the mobile phase. Apply separately to the plate 2 µl of each of the following 2 solutions in methanol R. For solution (A) shake a quantity of the powdered tablets equivalent to about 0.5 g of Ethambutol hydrochloride with 10 ml of methanol R for 5 minutes, filter, and use the filtrate. For solution (B) use 0.5 mg of aminobutanol R per ml of methanol R. After removing the plate from the chromatographic chamber, allow it to dry in air, heat at 105 °C for 5 minutes, cool, spray with triketohydrindene/cadmium TS, and heat again at 90 °C for 5 minutes. Examine the chromatogram in daylight.

Any spot corresponding to aminobutanol obtained with solution A is not more intense than that obtained with solution B.

B. *Note: The limits for Rifampicin related impurities are the maximum during the shelf-life of the finished pharmaceutical product.*

Carry out the test as described under "High-performance liquid chromatography" (Vol. 5, p. 257*), using the conditions given below under Assay method B.

Inject alternately 20 µl each of solutions A and C.

* Refers to The International Pharmacopoeia

In the chromatogram obtained with solution A the following peaks are eluted at the following relative retention with reference to rifampicin: rifampicin N-oxide = about 0.31; the hydrazone resulting from 3-formylrifamycin and isoniazid = about 0.55; rifampicin quinone = about 0.72; 3-formylrifamycin = about 0.87.

Measure the areas of the peak responses obtained in the chromatograms from solutions A and C, and calculate the content of the related substances as a percentage. In the chromatogram obtained with solution A, the area of the related impurity peak corresponding to the hydrazone peak is not greater than that obtained for the rifampicin peak with solution C (5.0%). No other peak is greater than half the area of the rifampicin peak obtained with solution C (2.5%). The sum of the areas of all the peaks, other than the principal peak, is not greater than twice the area of the rifampicin peak obtained with solution C (10.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution C. Disregard any peak with relative retention time less than 0.23 with reference to rifampicin.

Assay

Tests A and B are applicable.

A. Determine by "High-performance liquid chromatography" (Vol. 5, p. 257*), using a stainless steel column (15 cm x 4.6 mm) packed with *stationary phase A* (5 µm) (Luna® is suitable). As the mobile phase, use a solution prepared as follows: dissolve 50 g ammonium acetate R and 0.2 g copper(II) acetate R in 1000 ml of water and adjust to pH 5.0 ± 0.05 with glacial acetic acid R. Mix 940 ml of this solution with 60 ml methanol R.

Prepare the following solutions in water. For solution (A) weigh and powder 20 tablets. Transfer a quantity of the powder equivalent to about 100 mg ethambutol hydrochloride, accurately weighed, to a 500 ml volumetric flask. Dissolve in about 400 ml water by shaking for about 15 minutes. Dilute to 500 ml with water. Filter a portion of this solution through a 0.45 µm filter, discarding the first few ml of the filtered solution. For solution (B) dissolve 27.3 mg isoniazid RS, 145.5 mg pyrazinamide RS and 100 mg ethambutol hydrochloride RS in 500 ml water.

Operate with a flow rate of 2.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 270 nm.

Inject 20 µl of solution B. The test is not valid unless the resolution between the isoniazid and pyrazinamide peaks is not less than 2.

Inject separately 20 µl of solution B in replicate injections in the chromatographic system. The relative standard deviation for peak areas of isoniazid, pyrazinamide and ethambutol hydrochloride, eluting in this order, in replicate injections of solution B is not more than 2.0%.

Inject alternately 20 µl each of solutions A and B.

Measure the areas of the peak responses obtained in the chromatograms from solutions A and B, and calculate the percentage of isoniazid (C₆H₇N₃O), pyrazinamide (C₅H₅N₃O) and ethambutol hydrochloride (C₁₀H₂₄N₂O₂, 2HCl).

B. *Note: prepare fresh solutions and perform the tests without delay.*

Determine by "High-performance liquid chromatography" (Vol. 5, p. 257*), using a stainless steel column (25 cm x 4.6 mm) packed with *stationary phase A* (5 µm) (Luna® is suitable). As the mobile

* Refers to *The International Pharmacopoeia*

phase, use a mixture of 6 volumes of methanol R and 4 volumes of phosphate buffer pH 7.0 (potassium dihydrogen phosphate (0.1 mol/l), adjusted with sodium hydroxide (0.1 mol/l)).

Prepare the following solutions in methanol R. For solution (A) weigh and powder 20 tablets. Without delay, shake a quantity of the powder equivalent to about 150 mg Rifampicin in 100 ml methanol R, filter and dilute 5 to 50 ml with methanol R. For solution (B) use 0.15 mg rifampicin RS per ml. For solution (C) dilute a suitable volume of solution A to obtain a concentration equivalent to 7.5 µg Rifampicin per ml. For the system suitability test prepare solution (D) containing 0.15 mg rifampicin RS per ml and 7.5 µg rifampicin quinone RS per ml.

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

Inject 20 µl of solution D. The test is not valid unless the resolution between the peaks is not less than 4.

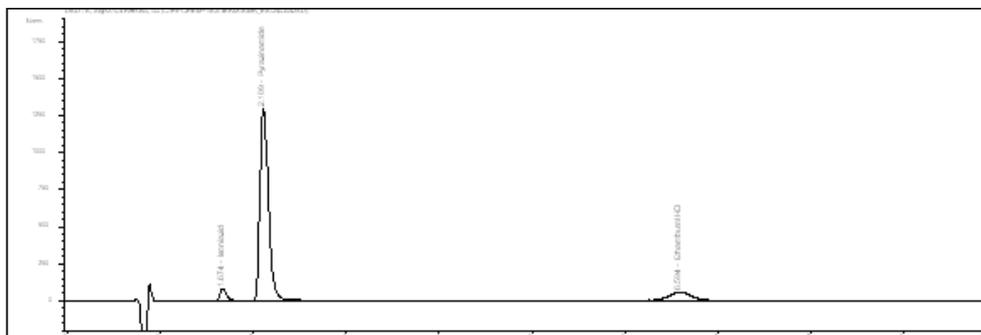
Inject separately 20 µl of solution B in replicate injections in the chromatographic system. The relative standard deviation for peak areas rifampicin in replicate injections of solution B is not more than 2.0%.

Inject alternately 20 µl each of solutions A and B.

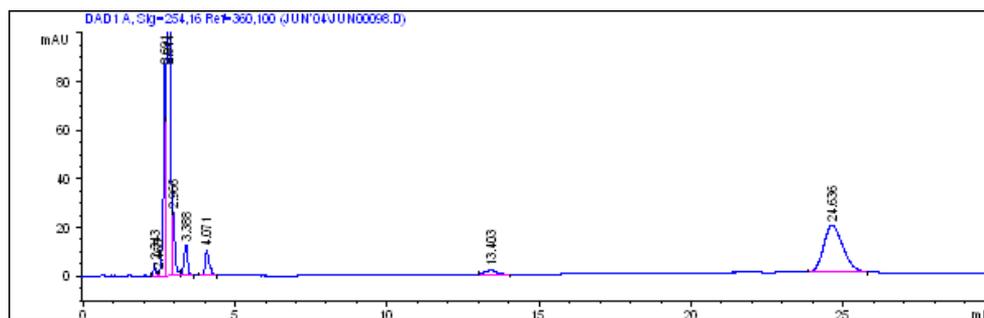
Measure the areas of the peak responses obtained in the chromatograms from solutions A and B, and calculate the percentage of rifampicin (C₄₃H₅₈N₄O₁₂).

Dissolution test. To be added.

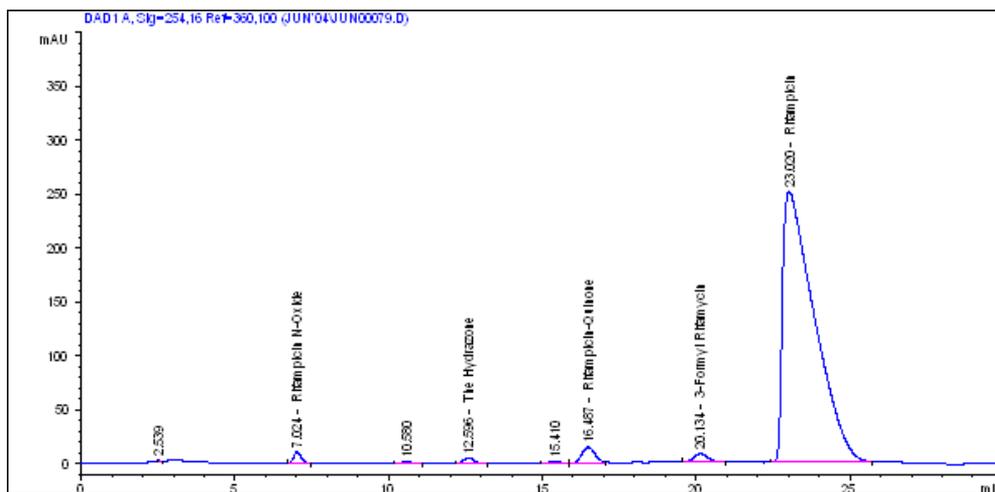
A typical chromatogram of isoniazid, pyrazinamide and ethambutol hydrochloride (4FDC product).



A typical chromatogram of rifampicin (4FDC product).



An example of a rifampicin concentrate spiked with degradants.



The International Pharmacopoeia: monographs for tuberculosis medicines

Rifampicin tablets (1st draft)

Within the framework of the Procurement, Quality and Sourcing Project for HIV, Tuberculosis and Malaria (<http://www.who.int/prequal>), *The International Pharmacopoeia* is collaborating with manufacturers, independent analytical drug quality control laboratories, national and regional pharmacopoeial bodies, research, governments, and regulatory bodies to provide specifications and monographs for tuberculosis medicines. A draft monograph for rifampicin tablets (below) is now being circulated for consultation. Please forward any comments to: Quality and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland or kopps@who.int.

Category. Antituberculosis drugs.

Storage. Rifampicin tablets should be packaged in airtight containers, protected from light.

Additional information. Strength in the current WHO Model List of Essential Medicines: 150 mg, 300 mg.

REQUIREMENTS

Complies with the monograph for "Tablets" (see Vol. 4, p. 26*).

Rifampicin tablets contain not less than 90.0% and not more than 110.0% of the amount of $C_{43}H_{58}N_4O_{12}$ stated on the label.

* Refers to *The International Pharmacopoeia*

Identity tests

Either test A alone or any two of tests B, C and D may be applied.

A. To a quantity of the powdered tablets equivalent to about 20 mg of Rifampicin add 5 ml of chloroform R and shake. Filter and evaporate the filtrate to dryness. Carry out the examination with the residue as described under "Spectrophotometry in the infrared region" (Vol. 1, p. 40*). The infrared absorption spectrum is concordant with the spectrum obtained from rifampicin RS or with the *reference spectrum* of rifampicin.

B. To a quantity of the powdered tablets equivalent to 1 mg of rifampicin add 3 ml of water, shake and filter. To the filtrate add 3 drops of copper(II) sulfate (160 g/l) TS, shake and heat to boiling; a violet colour is produced.

C. See test A described below under "Related substances". The principal spot obtained with solution F corresponds in position, appearance, and intensity with that obtained with solution E.

D. See test A described below under "Assay method". The retention time of the rifampicin peak in the chromatogram of solution A corresponds to that in the chromatogram of solution B.

Related substances

Either test A or test B may be applied.

A. Note: prepare fresh solutions and perform the test without delay.

Carry out the test as described under "Thin-layer chromatography" (Vol. 1, p. 83*), using silica gel R5 as the coating substance and a mixture of 85 volumes of chloroform R and 15 volumes of methanol R as the mobile phase. Apply separately to the plate 20 µl of each of the following 6 solutions in chloroform R. For solution (A) shake a quantity of the powdered tablets equivalent to about 0.1 g Rifampicin with 5 ml of chloroform R, filter, and use the filtrate. Prepare solutions containing (B) 0.80 mg of rifampicin quinone RS per ml, (C) 0.3 mg of rifampicin N-oxide RS per ml, (D) 0.10 mg of 3-formylrifamycin SV RS per ml and (E) 0.2 mg of the rifampicin RS per ml. For solution (F) dilute 1 volume of solution A to 100 volumes with chloroform R. After removing the plate from the chromatographic chamber, allow it to dry in a current of air and examine the chromatogram in daylight.

Any spots obtained with solution A, other than the principal spot, are not more intense than the corresponding spots obtained with solutions B (4.0%), C (1.5%) and D (0.5%). Furthermore, any other spots obtained with solution A are not more intense than that obtained with solution E (1.0%).

B. Carry out the test as described under "High-performance liquid chromatography" (Vol. 5, p. 257*), using the conditions given below under Assay method A.

Inject alternately 10 µl each of solutions A and C.

In the chromatogram obtained with solution A the following peaks are eluted at the following retention ratio with reference to rifampicin (approximate retention time = 25 to 30 min.): rifampicin N-oxide = about 0.27; rifampicin quinone = about 0.70; 3-formylrifamycin = about 0.87.

Measure the areas of the peak responses obtained in the chromatograms from solutions A and C, and calculate the content of the related substances as a percentage. In the chromatogram obtained with solution A, the area of the related substance peak corresponding to rifampicin quinone is not greater than that obtained for the Rifampicin peak with solution C (4.0%), the area of the related substance peak corresponding to Rifampicin N-oxide is not greater than 0.375 times the area of the Rifampicin

* Refers to *The International Pharmacopoeia*

peak with solution C (1.5%) and the area of the related substance peak corresponding to 3-formylrifamycin is not greater than 0.125 times the area of the rifampicin peak with solution C (0.5%). No other peak is greater than 0.25 times the area of the rifampicin peak obtained with solution C (1.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution C. Disregard any peak with retention ratio less than 0.23 with reference to rifampicin.

Assay

Either method A or method B may be applied.

A. Note: prepare fresh solutions and perform the tests without delay. Low-actinic glassware is recommended.

Determine by "High-performance liquid chromatography" (Vol. 5, p. 257*), using a stainless steel column (25 cm x 4.6 mm) packed with *stationary phase A* (5 µm) (Luna® is suitable). As the mobile phase, use a mixture of 6 volumes of methanol R and 4 volumes of phosphate buffer pH 7.0 (potassium dihydrogen phosphate (0.01 mol/l), adjusted with sodium hydroxide (0.1 mol/l)).

Prepare the following solutions in methanol R. For solution (A) weigh and powder 20 tablets, shake a quantity of the powder equivalent to about 0.15 g rifampicin, accurately weighed, in 100 ml methanol R, filter and dilute 5 ml to 10 ml with methanol R. For solution (B) use 0.75 mg rifampicin RS per ml. For solution (C) dilute a suitable volume of solution A to obtain a concentration equivalent to 30 µg rifampicin per ml. For the system suitability test prepare solution (D) containing 0.375 mg rifampicin RS per ml and 0.375 mg 3-formylrifampicin RS per ml.

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

Inject 10 µl of solution D. The test is not valid unless the resolution between the peaks is not less than 1.5.

Inject separately 10 µl of solution B in six replicate injections in the chromatographic system. The relative standard deviation of the peak area of Rifampicin is not more than 2.0%.

Inject alternately 10 µl each of solutions A and B.

Measure the areas of the peak responses obtained in the chromatograms from solutions A and B, and calculate the percentage content of rifampicin (C₄₃H₅₈N₄O₁₂).

A. Weigh and powder 20 tablets. Transfer a quantity of the powder equivalent to about 0.10 g of rifampicin, accurately weighed, to a 100-ml volumetric flask, add about 80 ml methanol R and shake. Dilute to volume with methanol R, mix, filter and discard the first 20 ml of the filtrate. Dilute 2 ml of the filtrate to 100 ml with phosphate buffer, pH 7.4, TS. Measure the absorbance of the resulting solution in a 1-cm layer at the maximum at about 475 nm, using as the blank phosphate buffer, pH 7.4, TS. Calculate the content of C₄₃H₅₈N₄O₁₂, using the absorptivity value of 18.7 (A_{1 cm}^{1%} = 187).

Dissolution test. To be added.

* Refers to *The International Pharmacopoeia*

The International Pharmacopoeia: monographs for tuberculosis medicines

Rifampicin and isoniazid tablets (1st draft)

Within the framework of the Procurement, Quality and Sourcing Project for HIV, Tuberculosis and Malaria (<http://www.who.int/prequal>), *The International Pharmacopoeia* is collaborating with manufacturers, independent analytical drug quality control laboratories, national and regional pharmacopoeial bodies, research, governments, and regulatory bodies to provide specifications and monographs for tuberculosis medicines. A draft monograph for rifampicin and isoniazid tablets (below) is now being circulated for consultation. Please forward any comments to: Quality and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland or kopps@who.int.

Category. Antituberculosis drugs.

Storage. Rifampicin and isoniazid tablets should be packaged in airtight containers, protected from light.

Additional information. Strengths in the current WHO Model List of Essential Medicines:

- 60 mg rifampicin and 30 mg isoniazid.
- 150 mg rifampicin and 75 mg isoniazid.
- 300 mg rifampicin and 150 mg isoniazid.
- 60 mg rifampicin and 60 mg isoniazid.
- 150 mg rifampicin and 150 mg isoniazid.

REQUIREMENTS

Complies with the monograph for "Tablets" (see Vol. 4, p. 26*).

rifampicin and Isoniazid tablets contain not less than 90.0% and not more than 110.0% of the amounts of rifampicin ($C_{43}H_{58}N_4O_{12}$) and isoniazid ($C_6H_7N_3O$) stated on the label.

Identity tests

Either test A and B or test C may be applied.

A. See the test described below under "Assay method A". The retention time of the Isoniazid peak in the chromatogram of solution A corresponds to that in the chromatogram of solution B.

B. See the test described below under "Assay method B". The retention time of the Rifampicin peak in the chromatogram of solution A corresponds to that in the chromatogram of solution B.

C. Carry out the test as described under "Thin-layer chromatography" (Vol. 1, p. 83*), using silica gel R5 as the coating substance and a mixture of 100 volumes of methanol R and 1.5 volumes of strong ammonia solution R as the mobile phase. Apply separately to the plate 2.5 ml of each of the following two solutions in methanol R. For solution (A) shake a quantity of the powdered tablets equivalent to about 5 mg Isoniazid for 15 minutes with 5 ml of methanol R, filter, and use the filtrate. For solution (B) use 1 mg isoniazid RS and a proportional quantity (according to the ratio in the tablet) of rifampicin RS per ml of methanol R. After removing the plate from the chromatographic chamber, allow it to dry in a current of air, place in a chamber with iodine vapours, and allow to stand for 20 minutes. Examine the chromatogram immediately in daylight.

* Refers to *The International Pharmacopoeia*

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

Related substances

Note: The limits for related substances are the maximum throughout the shelf-life of the finished pharmaceutical product.

Carry out the test as described under "High-performance liquid chromatography" (Vol. 5, p. 257*), using the conditions given below under Assay method B.

Inject alternately 10 µl each of solutions A and C.

In the chromatogram obtained with solution A the following peaks are eluted at the following retention ratio with reference to rifampicin (approximate retention time = 25 to 30 min.): rifampicin N-oxide = about 0.27; 3-(isonicotinoylhydrazinomethyl)rifamycin = about 0.52; rifampicin quinone = about 0.70; 3-Fformylrifamycin = about 0.87.

Measure the areas of the peak responses obtained in the chromatograms from solutions A and C, and calculate the content of the related substances as a percentage. In the chromatogram obtained with solution A, the area of the related substance peak corresponding to 3-(isonicotinoylhydrazinomethyl)rifamycin is not greater than that obtained for the rifampicin peak with solution C (5.0%). No other peak is greater than half the area of the rifampicin peak obtained with solution C (2.5%). The sum of the areas of all the peaks, other than the principal peak, is not greater than twice the area of the rifampicin peak obtained with solution C (10.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution C. Disregard any peak with retention ratio less than 0.23 with reference to rifampicin.

[Note of Secretariat: The limits for the related substances must still be finalized.]

Assay

Tests A and B are applicable.

A. Determine by "High-performance liquid chromatography" (Vol. 5, p. 257*), using a stainless steel column (15 cm x 4.6 mm) packed with *stationary phase A* (5 µm) (Luna® is suitable). As the mobile phase, use a solution prepared as follows: dissolve 50 g ammonium acetate R in 1000 ml of water and adjust to pH 5.0 ± 0.05 with glacial acetic acid R. Mix 940 ml of this solution with 60 ml methanol R.

Prepare the following solutions in water. For solution (A) weigh and powder 20 tablets. Transfer a quantity of the powder equivalent to about 30 mg Isoniazid, accurately weighed, to a 500 ml volumetric flask. Dissolve in about 400 ml water by shaking for about 15 minutes. Dilute to 500 ml with water. Filter a portion of this solution through a 0.45 µm filter, discarding the first few ml of the filtered solution. For solution (B) dissolve 30 mg isoniazid RS in 500 ml water.

Operate with a flow rate of 2.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 240 nm.

Inject separately 20 µl of solution B in six replicate injections in the chromatographic system. The relative standard deviation of the peak area of isoniazid is not more than 2.0%.

Inject alternately 20 µl each of solutions A and B.

Measure the areas of the peak responses obtained in the chromatograms from solutions A and B, and calculate the percentage content of isoniazid (C₆H₇N₃O).

* Refers to *The International Pharmacopoeia*

B. Note: prepare fresh solutions and perform the tests without delay. Low-actinic glassware is recommended.

Determine by "High-performance liquid chromatography" (Vol. 5, p. 257*), using a stainless steel column (25 cm x 4.6 mm) packed with *stationary phase A* (5 µm) (Luna® is suitable). As the mobile phase, use a mixture of 6 volumes of methanol R and 4 volumes of phosphate buffer pH 7.0 (potassium dihydrogen phosphate (0.01 mol/l), adjusted with sodium hydroxide (0.1 mol/l)).

Prepare the following solutions in methanol R. For solution (A) weigh and powder 20 tablets. Shake a quantity of the powder equivalent to about 0.15 g Rifampicin, accurately weighed, in 100 ml methanol R, filter and dilute 5 ml to 10 ml with methanol R. For solution (B) use 0.75 mg rifampicin RS per ml. For solution (C) dilute a suitable volume of solution A to obtain a concentration equivalent to 37.5 µg mg Rifampicin per ml. For the system suitability test prepare solution (D) containing 0.375 mg rifampicin RS per ml and 0.375 mg 3-formylrifampicin RS per ml.

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

Inject 10 µl of solution D. The test is not valid unless the resolution between the peaks is not less than 1.5.

Inject separately 10 µl of solution B in six replicate injections in the chromatographic system. The relative standard deviation of the peak area of Rifampicin is not more than 2.0%.

Inject alternately 10 µl each of solutions A and B.

Measure the areas of the peak responses obtained in the chromatograms from solutions A and B, and calculate the percentage content of rifampicin ($C_{43}H_{58}N_4O_{12}$).

Dissolution test. To be added.