

WHO Drug Information

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SWISSmedic

Announcement

**The 13th International Conference
of Drug Regulatory Authorities (ICDRA)
will be hosted by the Swiss Agency for
Therapeutic Products (Swissmedic) in
collaboration with the World Health
Organization**

**The ICDRA will take place
in Berne, Switzerland
from 16 to 19 September 2008**

**Updated information will be provided regularly at:
<http://www.icdra.ch>**

or

<http://www.who.int/medicines/icdra/en/index/html>

Pharmacovigilance Focus

Challenges of pharmacovigilance in Ukraine

Assuring the safety of medicinal products is a key component of Ukraine's national medicines policy. Activities involving safety and monitoring of adverse reactions are part of a pharmacovigilance system operated by the State Pharmacological Centre. Quality assurance of medicinal products remains the responsibility of the State Inspectorate for Quality Control of Medicinal Products.

In Ukraine, information provided by the pharmacovigilance system allows for the collection and scientific assessment of adverse reactions data reported following use of medicinal products. A fully functioning pharmacovigilance system is essential for providing scientific and evidence-based information to support regulatory decisions.

The pharmacovigilance system in Ukraine has been operational since 1996 and, over time, monitoring and reporting of adverse reactions has largely been integrated into the health care system through relevant legislation. The State Pharmacological Centre became a full member of the WHO Programme for International Drug Monitoring in 2002. Pharmacovigilance in Ukraine is currently based on European Union guidelines and rules governing medicinal products in the European Union which have been developed as a result of the International Conference on Harmonization (ICH) process (1, 2). These regulations have

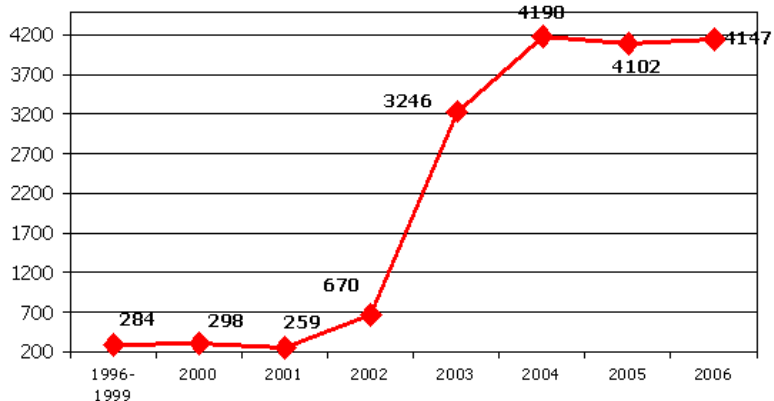
been translated and published in a book entitled *"Pharmaceutical Sector: Pharmacovigilance of Medicinal Products for Human Use"*(3). Regulatory guidance documents have also been issued to provide a framework for pharmacovigilance practices (4).

The early existence of an operational pharmacovigilance system in Ukraine greatly facilitated harmonization and introduction of European Union standards. A Ministry of Health Order (5) laid down future requirements for pharmacovigilance procedures with the aim of reinforcing medicines safety and ensuring access to effective and safe products for the population.

The State Pharmacological Centre coordinates all pharmacovigilance-related activities. Information on adverse reactions to medicinal products is processed and analysed by the Pharmacovigilance Department. This Department is also linked to Regional Centres where staff work with health care programmes and medical doctors throughout Ukraine. Department staff handle over 4000 cases of adverse reaction reports annually and during the period 1996–2006, the Pharmacovigilance Department received over 18 600 reports of adverse reactions to medicinal products (Figure 1, next page).

The Pharmacovigilance Department is responsible for the organization, methodology and educational activities related to pharmacovigilance. Since 2001, twenty-two workshops on organization and management have been held in Ukraine and were attended by over 2000 health care professionals. Participants included full-time specialists, chiefs of health departments of the State Adminis-

Article prepared by O.P. Viktorov, O.V. Matveyeva, I.O. Logvina. State Pharmacological Centre, Ministry of Health, Ukraine

Figure 1. Dynamics of adverse reaction reports received from doctors

trations, chief doctors, departmental heads, and physicians from different health care specialities in Ukraine. Four of these workshops dealt with establishment and implementation of a pharmacovigilance system targeting manufacturers of medicinal products.

In Ukraine, the spontaneous reporting system currently comprises:

- Methodologies and organizational activities managed by the Pharmacovigilance Department and Regional Centres;
- Collection of data on adverse reactions which is incorporated and utilized in generating state health statistics;
- Studies conducted during the postmarketing phase, which allow publication of safety profiles on selected medicinal products;
- Educational programmes for pre- and postgraduate training of doctors and pharmacists on collection and reporting of adverse reactions;
- Networking and links to international activities.

A book entitled *“Organization of the pharmacovigilance system in Ukraine”* was published in 2002 (6) describing the main objectives and resources needed to set up a pharmacovigilance system and the legislative basis required for conducting pharmacovigilance. Recommendations for doctors have also been published under the title *“Principles of reporting information about adverse reactions to medicinal products in human use”* (7). In addition, personnel from the Pharmacovigilance Department and Regional Centres have published more than 200 articles related to safety in medical journals.

The document *“Medicines Safety. Guidelines on Pharmacovigilance”* (8) urges pharmaceutical manufacturers, health practitioners, pharmacists, researchers, lecturers and students of medical and pharmaceutical colleges to take a more professional approach to safety issues.

Established in 2006, the magazine *“Rational Pharmacotherapy”* (9) reflects challenges and progress made in pharmacovigilance activities both in Ukraine and throughout the world. The magazine focuses on many of the changes in attitude taking place concerning use of medicinal products and patient safety.

Since the main source of adverse reaction reports is physicians, Ministry of Health Order 898 of 27 December 2006 instructs doctors to complete a reporting form (form 137/0) (4) and transmit this to the Regional Centre or directly to the State Pharmacological Centre (Figure 2).

In an effort to improve reporting of adverse reactions, the following activities have been identified as important by the State Pharmacological Centre:

- Promotion in all regions of Ukraine — through information, education and improved communications — of the importance of pharmacovigilance and adverse reaction reporting.
- Improving physician knowledge, attitude and behaviour of the need for organization and implementation of pharmacovigilance in health care settings.
- Identifying ways for health care facilities to promote and integrate systems of adverse reaction reporting by physicians.

- Fostering understanding and awareness of the importance of medicinal product safety through educational tools.
- Identifying new means of communication with administrators of health care facilities.
- Facilitating use of the reporting form. In this respect, the format and visual presentation have been revised. A new wording simplifies use and the improved form should now take a physician less than 10 minutes to complete.

Reporting adverse reactions is considered a civil and medical duty for doctors since delay in reporting could lead to or prolong the use of unsafe and inefficient medicinal products. The reporting form is now provided in two models: inpatient medical card and outpatient coupon, designed to facilitate reporting even further.

An important aspect of medicinal product safety is the close links which need to be forged between Ministry of Health staff,

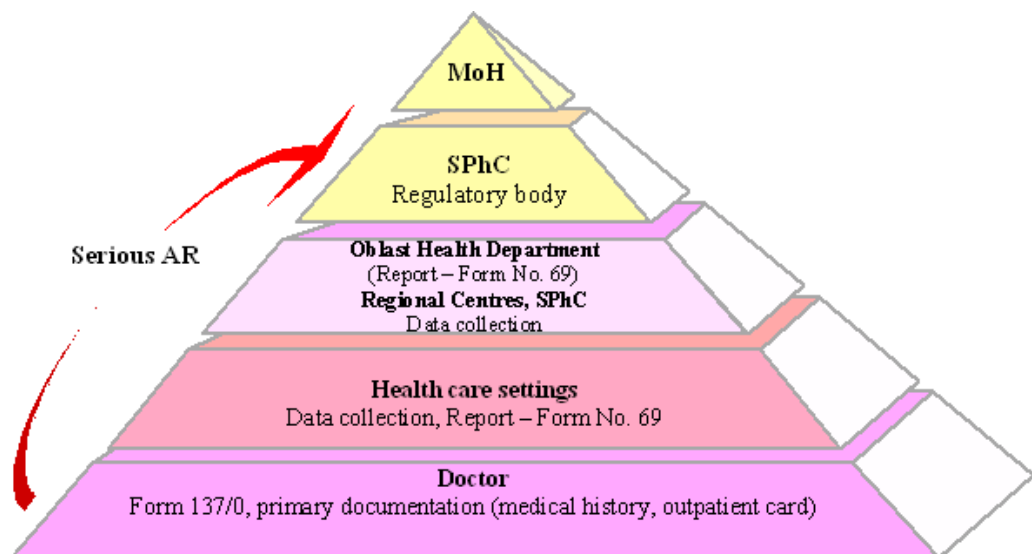


Table 1. Regulatory decisions taken in Ukraine on safety of medicinal products

Year	Name	Decision
1996	Phenacetin	Medical use banned
1996	Cimetidine	Medical use banned
1999	Hemodez	Medical use banned
2201	Phenylbutazone	Medical use limited
2002	Gentamycin	Medical use limited
2003	Nitrofurals	Medical use of oral dosage forms (tablets) banned
2003	Nitrofurans	Medical use limited
2003	Preparations containing kava-kava	Medical use banned
	Disintoxic solutions containing low-molecular polyvinylpyrrolidone	Medical use limited
2005	Metamizole sodium	Medical use limited
2005	Rofecoxib	Medical use limited
2005	Thioridazine	Medical use limited
2005	Euphylline	Medical use of dosage forms with ethylenediamine stabilizer banned

city health departments and health care facilities. Order 898 (4) also provides for chiefs of health care units to support pharmacovigilance activities of Regional Centres and the State Pharmacological Centre through training of health care workers in both regional and local settings. This means that, as a priority, heads of Regional Centres should be members of the health department review board and that heads of health departments and chief medical officers should be supportive of pharmacovigilance both at policy and implementation levels.

It should also be mentioned that Order 898 (4) sets out detailed requirements on pharmacovigilance for medicinal product manufacturers and their representatives, thus promoting a responsible attitude to safety of medicinal products. Compliance with these requirements is an obligatory condition for marketing the product in the country.

In Ukraine, the importance of safe medicinal products has now been addressed and legislative tools enacted. Establishment of structures to support regulatory mechanisms is under way and every effort is made for systems and processes to be compliant with European Union standards. It is hoped that the objectives of supporting rational pharmacotherapy will be promptly accomplished and expected improvements and outcomes achieved within an evidence-based, scientific context.

References

1. Directive of the European Parliament and European Council of 06.11.2001, 2001/83/EC. Regulation of the European Council of 22.07.93, 2309/93/EC.
2. The Rules Governing Medicinal Products in the European Union, Vol. 9 - Pharmacovigilance, Medicinal Products for Human Use and Veterinary Medicinal Products.

3. N.A. Liapunov, L.I. Kovtun, O.P. Besugla et al., Kyiv, Morion. *Pharmaceutical Sector: Pharmacovigilance of Medicinal Products for Human Use*. Eds. O.V. Stefanov, T.A. Bukhtiarova, V.I. Maltsev, V.G. Varchenko, O.P. Viktorov. 2003, p.216.
4. Ministry of Health, Ukraine, Order of 19.12.2000 No. 347 registered in the Ministry of Justice, Ukraine, 26.12.2000. Instructions for surveillance of adverse reactions/effects of medicinal products. Related Orders of 16.07.2001 No. 292; 08.02.2001 No. 51 & No. 52; 12.12.2001; and No. 497 registered in the Ministry of Justice, Ukraine, 28.12.2001.
5. Ministry of Health, Ukraine, Order of 28.12.2006 No. 898 registered in the Ministry of Justice, Ukraine, 29.01.2007.
6. O.V. Stefanov, O.P. Victorov, V.I. Maltsev, L.I. Kovtun, I.O. Logvina. *Organization of the pharmacovigilance system in Ukraine*. Kyiv, Avicena, 2002, p. 68.
7. V.M. Kovalenko, O.P. Viktorov, V.I. Maltsev et al. *Principles of reporting adverse reactions to medicinal products in human use. Methodological recommendations*. Kyiv, Avicena, 2004, p.55.
8. O.P. Viktorov, V.I. Maltsev, Yu.B. Belousova, *Medicines Safety. Guidelines on Pharmacovigilance*, Kyiv, Morion, 2007, p.240.
9. *Rational pharmacotherapy. Scientific and practical journal for physicians*. Kyiv, Zdorovje Ukrainy — XXI stoletije, LTD, 2006.

Adverse reaction reporting in Canada

Health Canada provides health professionals, consumers and patients with educational tools for reporting adverse reactions to drugs and other marketed health products, including prescription drugs; non-prescription drugs (including natural health products); biological products (including products derived from blood, biotech drugs, and therapeutic and diagnostic vaccines); and radiopharmaceuticals.

Health Canada has now developed two new educational modules on adverse reaction (AR) reporting of marketed health products. In addition to the existing module for naturopathic doctors, modules for other health professionals and for consumers are now available at the Learning Centre on the MedEffect website at [http://www..hc-sc.gc.ca](http://www.hc-sc.gc.ca)

The online module *Health Professional Reporting of Adverse (Drug) Reactions* provides an interactive tool to help health professionals report suspected adverse reactions. The online module for consumers, *Reporting Side Effects from Your Medicine: What You Need to Know*, comes with a guidebook and provides comprehensive learning tools to help consumers and patients report side effects.

Educational modules for health professionals reporting adverse reactions

Health Professional Reporting of Adverse Drug Reactions is a narrated, electronic (online) presentation to help health professionals recognize and report adverse reactions to Health Canada.

Reporting adverse reactions contributes to:

- The identification of previously unrecognized rare, or serious adverse reactions;
- Changes in product safety information;
- International data collection and dissemination regarding benefits, risks, and/or effectiveness of products.

Since 1965, health professionals have been reporting suspected adverse reactions to marketed health products to the Canadian Adverse Drug Reaction Monitoring Program.

Learning tools have now been developed to make it easier to report adverse reactions by increasing awareness about

how to report, what to report and how adverse reaction reports contribute to health safety.

A summary of the modules is set out below. The modules are available at the Medeffect website in the form of narrated, electronic presentations.

A vital link in the patient safety chain

After completing the learning modules and presentations, health professionals should be more knowledgeable about adverse reaction reporting and better able to:

- Describe an adverse reaction
- Associate adverse reaction reporting with your current work practice
- Describe the adverse reaction reporting process
- Report an adverse reaction

Some physicians have discontinued or changed their patients' medication regime due to adverse reactions associated with a particular drug. While this information is very valuable, it is often not reported because the physician or a member of the patient's health care team does not realize that the reaction should be reported, is unfamiliar with the reporting process or falsely believes that only proven adverse reactions should be reported.

With over 50% of newly approved therapeutic health products having serious side effects that are discovered only after the product is on the market, the need to report is critical. It has been estimated that for every adverse reaction that gets reported, up to 10 go unreported. It is for these reasons that there is a need to stimulate the reporting of adverse reactions by health professionals.

The module and reporting mechanism is presented in the form of a case presentation.

The case

A 32-year old male patient was diagnosed with depression. He was started on sertraline 50 mg daily. A week after starting therapy, he developed severe diarrhoea. He lost consciousness, fell and was admitted to hospital for rehydration.

While in hospital, sertraline was discontinued and the diarrhoea resolved. There are actually two problems here to deal with. First, what should be done for the patient and secondly how Health Canada is involved in the adverse reaction of this patient.

Before using another medical product, it is important to report this suspected adverse reaction. This patient is not taking any other prescribed medications and is not regularly using any OTC or natural health product. He is a young healthy man, with an unremarkable recent annual health exam. There is no relevant past history of concern. This is his first presentation of depression and there are a variety of therapeutic choices available for treatment.

Could this be an ADR? Health Canada describes an adverse reaction as a harmful and unintended response to a health product. This includes any undesirable effect suspected to be associated with the use of a health product. Examples of reportable undesirable effects include:

- Any unintended effect
- Health product abuse
- Overdose
- Interaction (including drug-drug and drug-food interactions)
- Any unusual lack of therapeutic efficacy

Suspected adverse reactions may be:

- serious
- unexpected
- in recently marketed products (< 5 years)

Reporting reactions, includes any reaction that is serious or seems unexpected, that is, if it's not consistent with the product information or labelling regardless of severity; and particularly any adverse reaction to a product that has been available for less than 5 years. A serious effect would require hospitalization or prolong an existing hospital stay; it may have caused congenital malformation, persistent or significant disability or incapacity; have required an intervention to prevent damage or permanent impairment, was life-threatening or resulted in death.

Where to start

There are a number of ways to report. There is a written form to fill in and send to Health Canada. The form is also available on-line at the MedEffect website. In addition to faxing or mailing in the form, a health professional can phone a toll free number and speak to someone who can take the information from the caller.

There are 4 pieces of information that must be entered on the form; an identifiable patient in **Section A**; a description of the reaction in **Section B**; a suspect health product in **Section C**, and an identifiable reporter in **Section D**.

Information on the identity of the patient and the reporter of the adverse reaction is kept strictly confidential. Personal information will not be disclosed to anyone except Health Canada personnel who need the information to carry out their responsibilities. Any requests for disclosure of the personal information would be dealt with according to the federal Privacy Act.

Patient information. The 'patient identifier' is reserved for the health professional in order to identify their patient in the event that follow-up is needed. A code, recognizable to the patient's health professional only, is best put here – no names.

For the present case patient, the adverse reaction is "severe diarrhoea with syncope requiring hospitalization". The words used to describe the adverse reaction are very important here as this description will get a medical code so the information can be retrieved from the database as needed.

Additional Information: The remaining fields add value to the report. They become indicators of causality to help Health Canada detect early warning signs.

Time-lines are very important – when the reaction took place, and when the patient started the drug. The evaluators working at Health Canada look at these reports to decide whether the suspected drug is likely to have caused the reaction. Indications of a temporal relationship are important. Also, the patient's health condition in the past, any relevant lab data, what happened when the patient stopped the drug, or if they started the drug again. All this information is very important to note. If a patient was taking other drugs or health products during the time of the adverse reaction, these products should be listed in the section calling for concomitant drugs. It is also good to write 'no other drugs taken' rather than leaving this space blank.

The form asks whether the reaction abated after use stopped or dose reduced. The severe diarrhoea did resolve once the patient was admitted and the sertraline was discontinued. This information field does not imply that the patient should be put back on the drug just to see if the reaction reappears. However, if the patient ends up coming back to this drug some time later, it would be useful follow-up information.

What does Health Canada do with the AR report form?

The adverse reaction report forms received are screened for the 4 minimum criteria mentioned earlier. When all 4 are present, the report is entered into the Canadian Adverse Drug Reaction Information System database.

The report is further assessed regarding the seriousness of the reaction, and a standard medical terminology is used to classify the reported information. Assigning standard medical terminology helps ensure that the same term is applied in similar situations reported.

Signals may be identified through the systematic review of adverse reaction reports plus any other additional information on product safety, and may be early indicators of a product-related issue. Detecting a safety signal triggers the need to investigate further a potential association between the product and the adverse reaction.

Medical evaluators use adverse reaction reports from the database (among other relevant sources of information) to determine if the suspect drug could have caused the reported reaction. Health professionals are encouraged to report their cases in as much detail as possible because it makes the information that much more valuable to the medical evaluators.

Products reported on the AR form: The type of health product to which this form applies include:

- prescription and non-prescription drugs
- natural health products
- radiopharmaceuticals, and
- biologics

Products not reported on this form

Vaccines (prevention of infectious disease)
Medical Devices

Preventative vaccines are monitored by the Public Health Agency of Canada. For these vaccines, health professionals should report to their local public health department.

An adverse reaction to a medical device gets reported to another part of Health Canada: the Health Products and Food Branch Inspectorate.

After reporting this reaction, an acknowledgment letter is sent thanking the reporter for their report and a reference or tracking number is given should any follow-up information become available or be needed at a later date, e.g., a biopsy or autopsy report, or any other clarification where needed.

Health Canada's adverse reaction informational resources

A number of reference documents are available to help with the reporting process and can be found in the MedEffect section of Health Canada's website <http://www.healthcanada.gc.ca/medeffect>. Some of the features which may be most clinically relevant are the most recent advisories, warnings and recalls, and the quarterly Canadian Adverse Reaction Newsletter.

Health Canada • Drugs & Health Products •

Home > Drugs & Health Products > MedEffect

MEdeffect
Together we can improve health product safety

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Report a Problem or Reaction

Search the Adverse Reaction Database

Sign-up for MedEffect e-Notice

Updates

Topics

- About MedEffect
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- Adverse Reaction Information
- Adverse Reaction Reporting
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- Canadian Adverse Reaction Newsletter (CARN)
- Consultations
- Frequently Asked Questions
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- Reports and Research
- Resource Centre
- Updates

About Health Canada

Consumer Product Safety

Diseases & Conditions

Drugs & Health Products

- Adverse Reaction Information
- Advisories, Warnings & Recalls
- Biologics, Radiopharmaceuticals & Genetic Therapies
- Compliance & Enforcement
- Controlled Substances & Precursor Chemicals
- Drug Products
- International Activities
- MedEffect
- Medical Devices
- Medical Use of Marijuana

WHO pharmacovigilance capacity building

The WHO Programme for International Drug Monitoring is supporting a three-way approach to international pharmacovigilance training by providing:

1. Generic pharmacovigilance training for participants from different parts of the world.
2. National training courses, tailored to the specific needs of each country, and customized to include safety surveillance of specific disease programmes.
3. A synthesis of the two approaches to include capacity building for a group of countries with very similar disease burdens and pharmacovigilance interests. This would have the advantage of providing a regional pool of expertise.

Recent activities

Botswana — A pharmacovigilance training course was organized in September 2006 in Gaborone. Ten drug regulatory officials attended the week-long course and were trained in the basic principles of pharmacovigilance, reporting systems, adverse drug reactions (ADR) database, tools for ADR data management, causality assessment, signal detection, preventing and managing ADRs, cohort-event monitoring and communications in pharmacovigilance.

The course included practical methods for setting up a pharmacovigilance system and liaising with public health programmes. Working groups compared various national reporting forms.

Morocco — A pharmacovigilance training course was organized in February 2007 for Francophone countries and included participants from Algeria, Benin, Burkina Faso, Cameroun, Côte d'Ivoire, Democratic Republic of Congo, Gabon, Madagascar, Mali, Morocco, Sao Tomé-et-Principe, Senegal, Togo and Tunisia.

Zambia — A follow-up course was held in February 2007 with participants from Burundi, Democratic Republic of Congo, Mozambique, Zambia and Zanzibar. This followed on from a course in 2003 which introduced pharmacovigilance to countries about to introduce artemisinin-based combination therapies (ACTs).

At this meeting, countries identified three areas for action:

- the need to prioritize and strengthen pharmacovigilance activities;
- the need to advocate pharmacovigilance issues at regional level through regional economic bodies; and
- the need to harmonize national ADR reporting forms and guidelines for spontaneous reporting, in particular in Malaria Case Management training manuals and guidelines.

WHO is currently preparing two training programmes in Ghana devoted to teaching the basic principles of cohort event monitoring and developing a final protocol to collect ADR reports in the national malaria programmes. Additionally, participants will learn about other problems that could arise in pharmacovigilance.

Reference: World Health Organization. Feature. *WHO Pharmaceuticals Newsletter*, No. 3, 2007.

Safety and Efficacy Issues

Rosiglitazone: cardiac safety

Canada — An article recently published in the *New England Journal of Medicine* (NEJM) has generated significant public attention on the cardiac safety of the antidiabetic rosiglitazone (Avandia®, Avandamet® and Avandaryl™). The article (1), based on a meta analysis of 42 clinical studies, noted a statistically significant increased risk of myocardial infarction and a statistically non-significant increase in the risk of cardiovascular death associated with the use of rosiglitazone in comparison to placebo or other anti-diabetic therapies. The conclusions reached require confirmation. Analysis of all currently available data is ongoing and findings will be communicated when a review is complete.

Some of the studies in the *NEJM* article included patients using rosiglitazone in combination with other anti-diabetic therapies. Some of these combinations, specifically rosiglitazone + metformin + sulfonylurea or rosiglitazone + insulin are not approved for use in Canada.

In Canada, Avandia® is NOT approved for use with insulin therapy; with the combination of metformin AND a sulfonylurea; or in patients with pre-diabetes (2).

Avandia® is contraindicated in patients with Class III and IV cardiac status. Avandia® should be used with caution in any patient with NYHA Class I and II cardiac status. All patients should be monitored for signs and symptoms of fluid retention, edema, and rapid weight gain. The dose of Avandia® used in combination with a sulfonylurea should not exceed 4 mg daily.

In Canada, Avandia® is indicated for:

- use as monotherapy in patients not controlled by diet and exercise alone, to reduce insulin resistance and lower elevated blood glucose in patients with type 2 diabetes mellitus.
- use in combination with metformin or a sulfonylurea when diet and exercise plus the single agent do not result in adequate glycemic control. For patients inadequately controlled on metformin or a sulfonylurea, Avandia® should be added to, not substituted for, metformin or the sulfonylurea.

Treatment with thiazolidinediones has been associated with cases of congestive heart failure, some of which were difficult to treat unless the medication was discontinued. Avandia® should be discontinued if any deterioration in cardiac status occurs.

References

1. Nussen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New England Journal of Medicine*, **356**: 2457-71, 2007.
2. Communication from GlaxoSmithKline, 1 June 2007 at <http://www.hc-sc.gc.ca>

European Union — The European Medicines Evaluation Agency (EMA) has reminded physicians that when rosiglitazone was first authorized in the European Union in 2000, it was contraindicated in patients with a history of cardiac failure. Since then, EMA has closely monitored rosiglitazone for cardiovascular effects.

The EU rosiglitazone product information was updated in September 2006 with information about the risk of ischaemic events. Prescribers are reminded to adhere to the restrictions for use in patients with cardiac disease as set out in the product information. Patients are advised not to stop treatment with rosiglitazone, but to discuss the medication with their doctor.

Reference: Press release. EMEA, 23 May 2007 at <http://www.emea.europa.eu>

Rosiglitazone: cardiovascular safety profile

Singapore — Rosiglitazone (Avandia®) is an oral agent for the treatment of type 2 diabetes mellitus registered by the Health Sciences Agency (HSA) since 2000 for use as an adjunct to diet and exercise, as monotherapy, or in combination with metformin or a sulfonylurea to reduce insulin resistance and lower elevated blood glucose in patients with type 2 diabetes mellitus. Avandamet® is another registered product containing a combination of two active ingredients, rosiglitazone and metformin.

The risk of cardiac adverse events (i.e. heart failure, fluid retention, oedema) is known to be associated with the thiazolidinediones class of drugs. Recently, concerns have been raised about the possible elevation of ischaemic cardiovascular (CV) risk with rosiglitazone therapy.

The findings of a study published in the *New England Journal of Medicine* on 21 May 2007 have caused considerable debate. Two additional studies have been conducted. The various studies provide contradictory findings on the ischaemic CV risk of rosiglitazone (1–3). HSA will continue to keep rosiglitazone under close surveillance for CV effects (i.e. cardiac failure, myocardial infarction) and monitor the international developments in

this area. Healthcare professionals will be updated on new developments in this area when the data becomes clearer.

In the interim, prescribers should continue to carefully make individualised treatment decisions for patients with diabetes mellitus. It is advised that patients on Avandia® should be monitored for signs and symptoms of heart failure, fluid retention, oedema and rapid increases in weight.

Source: Product Safety Alert, 26 July 2007. <http://www.hsa.gov.sg/cda/safetyalerts>

References

1. *N Engl J Med* 2007 Jun 14; **356**(24):2457-71 (Epub May 21).
2. *N Engl J Med* 2007 (Epub Jun 5).
3. *N Engl J Med* 2006 Dec 7; **355**(23):2427-43.
4. *Lancet* 2006 Sept 23; **368**:1096-105.

Bevacizumab: tracheo-oesophageal fistula

Canada — Important new safety information regarding use of bevacizumab (Avastin®) has been released. Bevacizumab is a recombinant humanized monoclonal antibody that is directed against the vascular endothelial growth factor (VEGF). It is authorized for first-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with fluoropyrimidine based chemotherapy.

Based on a review of post market and clinical trial reports serious adverse events, including fatal events, of tracheo-oesophageal (TE) fistula have been reported in association with use of bevacizumab in clinical trials of small cell lung cancer (SCLC), non small cell lung cancer (NSCLC) and esophageal cancer. Bevacizumab should be permanently

discontinued in patients with tracheo-esophageal (TE) fistula or any gastrointestinal fistula. There is limited information on the continued use of bevacizumab in patients with other fistulas. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

Reference: Medeffect 1 June 2007 at <http://www.hc-sc.gc.ca>

NSAIDs and cardiovascular risk

Singapore — Following worldwide voluntary withdrawal of rofecoxib (Vioxx®) in October 2004 due to concerns of an increased cardiovascular (CV) risk, HSA and its Expert Advisory Committee has reviewed the CV risks of the entire class of non-steroidal anti-inflammatory drugs (NSAIDs).

Based on the available data in April 2005, HSA concluded that the coxibs or the newer COX-2-selective inhibitors, namely rofecoxib, celecoxib, and etoricoxib, were associated with an increased risk of CV events and that the risk increased with higher dose and duration of use. HSA also strengthened the local package inserts of these products to contraindicate the perioperative use of these drugs in patients who have recently undergone coronary artery bypass graft (CABG) surgery and revascularisation procedures. At that time, due to the lack of information on the CV risks for the older NSAIDs, HSA concluded that the possibility of similar CV risk could not be ruled out although there was insufficient data to show that the older NSAIDs pose similar CV risks as the coxibs.

Recently, the availability of several well conducted meta-analyses of randomised trials, case-control and cohort studies involving the older NSAIDs have provided regulators with a better means of assessing the safety profile of these drugs. HSA

and its Pharmacovigilance Advisory Committee (PVAC) have reviewed these data and taking into account international regulatory developments, arrived at the following recommendations on the CV risks and the use of this class of drugs:

- Non-selective NSAIDs are important treatments for arthritis and other anti-inflammatory and painful conditions.
- Non-selective NSAIDs may be associated with a small increase in the absolute risk of cardiovascular events (e.g. myocardial infarction and stroke), especially when used at high doses for long-term treatment.
- All NSAIDs should be prescribed at the lowest effective dose and the duration of treatment should be periodically reviewed and kept as short as possible.
- All NSAIDs should not be used peri-operatively in patients who have recently undergone coronary artery bypass graft (CABG) surgery and revascularisation procedures.

HSA will be working with the relevant drug companies to strengthen the labeling information in the package inserts of the older NSAIDs to reflect the CV safety concerns.

Source: Product Safety Alert, 26 July 2007. <http://www.hsa.gov.sg/cda/safetyalerts>

References

1. *BMJ* 2006 Jun; **332**:1302-08.
2. *JAMA* 2006 Oct; **296**:E1-E12.
3. *Basic Clinic Pharmacol Toxicol.* 2006 Mar; **98**(3):266-74.
4. *Pharmacotherapy* 2006 Oct; **26**:1379-87.
5. *Eur Heart J* 2006 Jul; **27**:1657-63.

Rosiglitazone and parotid gland enlargement

Canada — The thiazolidinedione rosiglitazone (Avandia®) is an insulin sensitizer that is indicated for use either as monotherapy or in combination with metformin or a sulfonyleurea in patients whose type 2 diabetes is inadequately controlled by diet and exercise alone (1). In the January 2006 issue of the *Canadian Adverse Reaction Newsletter*, it was reported that Health Canada had received 5 domestic reports of parotid gland enlargement suspected of being associated with the use of rosiglitazone (2). As of December 2006, 1 additional domestic report was received. All 6 cases involved patients who experienced visibly evident enlargement of one or both parotid glands while taking the drug. In 4 cases, the adverse reaction was alleviated or resolved when rosiglitazone therapy was stopped; in the remaining 2 cases this information was not provided.

The parotid glands are the largest of the salivary glands and are located in the facial subcutaneous tissue, over the posterior aspect of each mandibular ramus. There is considerable variation in the size of parotid glands of healthy individuals (3), but on clinical examination they are not visible and are not readily palpable. Nontender parotid gland enlargement has been associated with a number of medical disorders and medications (4–7).

Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor gamma (1) and binding of rosiglitazone seems to be an important component of its mechanism of action (8).

Extracted from Canadian Adverse Reaction Newsletter, Volume 17(3), July 2007.

References

1. Avandia (rosiglitazone) [product monograph]. Mississauga (ON): GlaxoSmithKline Inc.; 2006.
2. Health Canada. Rosiglitazone (Avandia): suspected association with parotid gland enlargement. *Can Adverse Reaction News* 2006;**16**(1):3.
3. Medbery R, Yousem DM, Needham MF, et al. Variation in parotid gland size, configuration, and anatomic relations. *Radiother Oncol* 2000;**54**(1):87–9.
4. Daniels TE. *Diseases of the mouth and salivary glands*. In: Goldman L, Ausiello D editors. Cecil textbook of medicine. 22nd edition. Philadelphia: Saunders; 2004. p. 2426–32.
5. Russotto SB. Asymptomatic parotid gland enlargement in diabetes mellitus. *Oral Surg Oral Med Oral Pathol* 1981;**52**(6):594–8.
6. Gill G. Metabolic and endocrine influences on the salivary glands. *Otolaryngol Clin North Am* 1977;**10**(2):363–9.
7. *Infectious diseases, Mumps*. In: Porter RS, Kaplan JL, eds. The Merck manual online. Available: www.merck.com/mmpe/index.html.
8. Wagstaff AJ, Goa KL. Rosiglitazone: a review of its use in the management of type 2 diabetes mellitus. *Drugs* 2002;**62**(12):1805–37.

Cinacalcet: indication changes

Canada — The manufacturer of cinacalcet hydrochloride (Sensipar®) has announced that the product is no longer indicated for chronic kidney disease patients (stages 3 and 4) not receiving dialysis.

Sensipar® was authorized by Health Canada on 9 August 2004 for the treatment of secondary hyperparathyroidism in patients with Chronic Kidney Disease (CKD). Cinacalcet controls parathyroid hormone levels, calcium and phospho-

rous levels, and the serum calcium-phosphorous product in patients with CKD. This indication included patients with CKD receiving dialysis and not receiving dialysis.

Use of Sensipar® in patients with secondary hyperparathyroidism and CKD not receiving dialysis is no longer indicated.

Reference: Communication to healthcare professionals. 19 June 2007 at <http://www.hc-sc.gc.ca>

Omalizumab and anaphylaxis

United States of America — A New Medication Guide on the risk of anaphylaxis following administration of omalizumab (Xolair®) has been distributed. Omalizumab is approved to treat adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aero-allergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

Reference: *FDA Press Release: FDA Proposes to Strengthen Label Warning for Xolair and FDA Alert*, 21 February 2007; updated 5 July 2007

Vinca alkaloids: intravenous administration

France — The French Agency for Safety of Medicines and Health Products (AFSSAPS) has reminded healthcare professionals that the chemotherapeutic agents vindesine, vincristine and vinblastine are to be given only by intravenous and not intrathecal route.

Between 2000 and 2006, the Agency received seven reports of administration errors where vinca alkaloids were given by intrathecal route. Six of these errors were reported in adult patients and one in a child of 23 months. The patients died in all seven cases.

Reference: Communication to healthcare professionals. Afssaps, May 2007 <http://www.afssaps.sante.fr>

Pioglitazone: fractures in women

Switzerland/Canada,France — The manufacturers of pioglitazone have informed health care professionals of the increased incidence of fractures in women receiving long-term treatment with pioglitazone for type 2 diabetes. Pioglitazone belongs to the thiazolidinedione (TZD) group of antidiabetic medicines.

An analysis of the pioglitazone clinical trial database, with a special focus on fractures reported as adverse events, has shown that significantly more pioglitazone-treated female patients experienced at least one event of bone fracture than patients treated with non-TZD comparator drugs (other diabetes medicines such as metformin or sulfonylureas or placebo). The majority of the fractures involved distal lower limb: ankle, foot, or distal upper limb: hand, forearm and wrist.

References

1. Switzerland. Communication from Takeda, 5 April 2007. <http://www.swissmedic.ch>
2. Canada. Communication from Eli Lilly, 18 April 2007. <http://www.hc-sc.gc.ca>
3. France. Communication from Takeda, 19 April 2007. <http://www.afssaps.fr>

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.

Regulatory Action and News

Viracept®: suspension pending quality and safety assessment

European Union — The European Commission has suspended the marketing authorization for Viracept® (INN - nelfinavir) (1). Nelfinavir is an antiretroviral medicine used to treat HIV-1 infected adults, adolescents and children of three years of age and older.

The current suspension follows a Press Release from EMEA (2) that Viracept® was being recalled by the manufacturer due to the presence of a genotoxic substance, ethyl mesylate, in some batches of the product. In agreement with the manufacturer, EMEA has outlined a specific action plan to follow-up patients exposed to the contaminated product.

As the contamination may have affected all strengths and presentations of Viracept®, the company has undertaken a recall of this product in all territories except USA, Canada and Japan. Patients receiving this product should contact their doctor immediately for advice on appropriate treatment alternatives.

References

1. Press Release. European Medicines Agency, EMEA/275367/2007, 21 June 2007. <http://www.emea.europa.eu> and Commission Decision C(2007)3865 6 August 2007.
2. Press Release. European, Medicines Agency, EMEA/251283/2007, 6 June 2007 <http://www.emea.europa.eu>

World Health Organization — Viracept® was prequalified by WHO based on a scientific evaluation of the European Medicines Agency (EMA). Following the

recall of Viracept® (nelfinavir) by the manufacturer (3), WHO has temporarily suspended Viracept® from the list of prequalified products and has issued the following advice.

Nelfinavir belongs to the Protease Inhibitor (PI) class of antiretroviral medicines. Current stocks of Viracept® should be quarantined and all remaining formulations returned to the manufacturer (4).

Countries that have included Viracept® in post-exposure prophylaxis packs should remove and replace it with a suitable boosted protease inhibitor. If no boosted PI is available, dual nucleoside therapy without a PI will remain effective. Adults or children currently taking Viracept® should not interrupt their antiretroviral therapy. However, they should see their antiretroviral provider as soon as possible, to change to a suitable alternative. Updated information can be obtained at: <http://www.who.int/prequal>

The following protease inhibitors are adequate within-class substitutions for nelfinavir: lopinavir/ritonavir (LPV/r), indinavir/ritonavir (IDV/r), saquinavir/ritonavir (SQV/r), atazanavir/ritonavir (ATV/r), and fosamprenavir/ritonavir (FPV/r). LPV/r is the preferred boosted PI, as it has the advantage of being available as a fixed-dose combination and has recently been approved in a new heat-stable formulation, which eliminates the need for refrigeration. In children, SQV is only licensed for use in children over 25 kg. ATV and FPV are not yet approved for use in children.

Nelfinavir is sometimes used as part of initial therapy for pregnant women. If this is the case and no other PI is available, then substitution of Viracept® by another

active ARV from another class of drugs should be considered. Non-nucleoside reverse transcriptase inhibitors need to be used with caution in pregnant women.

In summary, for patients needing to substitute Viracept®, options include:

- a boosted protease inhibitor;
- nevirapine – with close observation for toxicity if CD4 is above 250 cells/mm³;
- efavirenz – unless in the first trimester of pregnancy;
- triple nucleoside therapy.

References

1. WHO Statement on Roche's Viracept® recall. WHO Prequalification Programme, 14 June 2007. <http://mednet3.who.int/prequal>
2. WHO Information Exchange System Alert No. 114, 11 June 2007. <http://www.who.int/medicines/publications/drugalerts/en/index.html>
3. Suspension of Viracept® from the list of WHO prequalified products. WHO Prequalification Programme, 21 June 2007. <http://mednet3.who.int/prequal>
4. Demand Manager F.Hoffmann-La Roche Ltd., Basel, Building 237/2.17; CH 4303 Switzerland Phone: +41 61 688 9390; Fax: +41 61 687 1815; e-mail: sandra.torriani_cazzato@roche.com

Nimesulide: suspension following liver failure

Ireland —The Irish Medicines Board (IMB) has announced suspension of nimesulide containing medicinal products for oral use with immediate effect (1). The suspended products include Aulin®, Mesulid® and Mesine®. The decision was based on information from a National Liver Transplant Unit concerning six patients requiring liver transplant following treatment with nimesulide.

Nimesulide is a nonsteroidal anti-inflammatory agent for the treatment of acute pain, symptomatic treatment of painful osteoarthritis and primary dysmenorrhoea. Liver damage is a serious and rare event known to occur with nimesulide. IMB had previously issued advice to healthcare professionals on this risk.

The IMB has received 53 liver-related adverse reaction reports with nimesulide since the product was first approved for use in Ireland in 1995.

Reference: Press Release from the Irish Medicines Board, 15 May 2007 <http://www.imb.ie>

World Health Organization — WHO has issued a Drug Alert based on the IMB decision to suspend oral nimesulide-containing products from the Irish market. In 2003 the Committee for Proprietary Medicinal Products (CPMP) of the European medicines Agency (EMA) considered the benefit-risk profile of nimesulide-containing products.

The WHO Adverse Reactions Database reports a total number of 320 cases of liver and biliary system disorders in patients who received nimesulide. Of these, 18 cases have been associated with nimesulide use.

Reference: *WHO Information Exchange System Alert No. 113*, <http://www.who.int/medicines/publications/drugalerts>).

Singapore — The Health Sciences Authority (HSA) is suspending sale of oral preparations containing the nonsteroidal anti-inflammatory drug, nimesulide.

This suspension is being taken as a precautionary measure in view of new information suggesting an increased risk of liver toxicity compared to other drugs in the same class. HSA will be conducting a more in-depth risk-benefit assessment of the drug following this suspension.

Nimesulide is a nonsteroidal anti-inflammatory drug (NSAID) available since 1999. Currently there are five nimesulide-containing products registered locally, namely Nidol® Tablet, Nidol® Satchet, Nimotas-CD® Tablet, Nise® Tablet and Qnim MD® Tablet. They are regulated as prescription only medicines and are licensed for the treatment of acute pain, symptomatic treatment of painful osteoarthritis and primary dysmenorrhoea.

The local adverse drug reaction database noted isolated reports of liver toxicity associated with nimesulide. However, the adverse reactions could not be attributed directly to the drug because of the presence of concurrent medications. As nimesulide is not a widely prescribed drug in Singapore and there are many other alternative treatment options available, HSA has assessed that it would be prudent to suspend the sales of these products pending a review by the European Medicines Agency, EMEA.

Reference: *HSA Press Release*, 15 June 2007 at <http://www.hsa.gov.sg/cda/safetyalerts>

Tegaserod temporarily suspended

Singapore — The Health Sciences Authority (HSA) has requested the manufacturer (Singapore) to temporarily withhold sales of tegaserod (Zelmac®) (1). This measure has been taken to permit further evaluation of new safety information submitted by the manufacturer and reassessment of risk/benefit. Marketing and sales of tegaserod have also been suspended in the US and Canada (2).

HSA advises patients taking tegaserod to stop taking the drug and consult their doctor to discuss alternative treatment options for their condition. Patients who are taking tegaserod and experiencing

severe chest pain, shortness of breath, dizziness, sudden onset of weakness or difficulty walking or talking or other symptoms of heart attack or stroke, should seek immediate medical attention.

Reference: *HSA Product Safety Alert*, 3 April 2007 at <http://www.hsa.gov.sg/cda/safetyalerts>

Withdrawal of products containing veralipride

European Union — The European Medicines Agency (EMA) has recommended the withdrawal of all medicinal products containing veralipride. EMA made this recommendation following advice from the Committee for Medicinal Products for Human Use (CHMP) that the risks of veralipride in the treatment of hot flushes associated with menopause are greater than its benefits.

The CHMP has assessed all available information on the safety and efficacy of veralipride and has concluded that while veralipride shows limited efficacy, it is associated with side-effects, including depression, anxiety, and tardive dyskinesia (a movement disorder which may be long lasting or irreversible), both during and after treatment. The CHMP undertook this assessment following a request from the European Commission in September 2006 when veralipride was withdrawn from the Spanish Market due to reports of serious nervous system disorders.

EMA advises patients taking veralipride for the treatment of hot flushes to consult their doctor. Veralipride treatment should not be stopped abruptly but the dose reduced gradually.

Reference: EMA Press Release, European Medicines Agency Press Office, 19 July 2007. <http://www.emea.europa.eu>

Current Topics

Global strategy to prevent transmission of Chagas disease

Chagas disease is a serious, potentially life-threatening illness caused by the protozoan parasite *Trypanosoma cruzi*. It is mainly transmitted by large blood-sucking insects. The parasite can also be transmitted by blood transfusion or organ transplant from infected donors, and occasionally by transplacental passage from infected mother to newborn baby. Early symptoms include fever, fatigue, swollen glands and heart pain, but in later years the infection can lead to chronic debilitation caused by progressive destruction of the heart muscle.

Latin American countries have made enormous efforts to control the infection, and current estimates suggest that under 8 million people remain infected. In some regions of South America, chronic infection can also give rise to severe intestinal problems requiring corrective surgery.

However, because of blood transmission and organ transplantation, the infection is no longer confined to the Americas. Cases have been identified in non-endemic countries in Europe, Canada and the United States.

During a meeting of experts and partners held in Geneva in July 2007, WHO has launched a new effort to eliminate Chagas disease by 2010. The WHO Global Network for Chagas Elimination has been established to coordinate global activities and a strategy has been outlined on treatment and control. The network, is comprised of technical groups of experts who will develop a five-pillar strategy and focus on several key aspects of transmission, including:

- strengthening epidemiological surveillance and information systems;
- preventing transmission through blood transfusion and organ transplantation in endemic and non-endemic countries;
- identifying a diagnostic test(s) for screening and diagnosis of infections;
- expanding secondary prevention of congenital transmission and case management of congenital and non-congenital infections; and
- promoting a consensus on adequate case management.

Efforts to eliminate Chagas disease will be enhanced by the pharmaceutical industry, which is providing financial support to the network and provision of one of the medicines used for the disease.

The establishment of the network occurs within the broader context of WHO's goal to address neglected tropical diseases. Cases identified in non-endemic countries have demonstrated the need to globalize efforts. The WHO Region of the Americas has achieved success in eliminating vector-borne transmission of Chagas disease. Now, however, it is important to reduce risk of transmission from blood or blood products obtained from migrants from areas endemic for Chagas disease, and to ensure screening and diagnosis of congenital Chagas disease.

Reference: *Weekly Epidemiological Record*, **82**(28/29): 259–261 (2007). <http://www.who.int/wer>

Consultation Documents

International Pharmacopoeia

Amodiaquine hydrochloride tablets

Draft proposal for the *International Pharmacopoeia* (June 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax +4122791 4730 or e-mail to rabhouansm@who.int

Category. Antimalarial.

Storage. Amodiaquine hydrochloride tablets should be kept in a well-closed container.

Labelling. The designation of the container of Amodiaquine hydrochloride tablets should state that the active ingredient is in the hydrochloride form and the quantity should be indicated in terms of the equivalent amount of amodiaquine.

Additional information. Strength in the current WHO Model list of essential medicines: 153 mg and 200 mg of amodiaquine (as hydrochloride).

153 mg of amodiaquine is approximately equivalent to 200 mg of amodiaquine hydrochloride (2HCl, 2H₂O); 200 mg of amodiaquine is approximately equivalent to 260 mg of amodiaquine hydrochloride (2HCl, 2H₂O).

REQUIREMENTS

Comply with the monograph for "Tablets".

Definition. Amodiaquine hydrochloride tablets contain Amodiaquine hydrochloride. They contain not less than 90.0% and not more than 110.0% of the amount of amodiaquine (C₂₀H₂₂ClN₃O) stated on the label.

Identity tests

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

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

A.1. Carry out the test as described under 1.14.1 Thin-layer chromatography. Prepare a solution of chloroform saturated with ammonia by shaking chloroform R with ammonia (~260 g/l) TS and separate the chloroform layer. Use silica gel R6 as the coating substance and a mixture of 9 volumes of chloroform saturated with ammonia, and 1 volume of dehydrated ethanol R as the mobile phase. Apply separately to the plate 2 il

of each of the following two solutions in chloroform saturated with ammonia. For solution (A) shake a quantity of the powdered tablets containing the equivalent of about 0.15 g amodiaquine with 10 ml vigorously for 2 minutes in a glass-stoppered test-tube, filter through a 0.45 filter and use the filtrate. For solution (B) shake 20 mg of amodiaquine hydrochloride RS per ml vigorously for 2 minutes in a glass stoppered test-tube, allow the solids to settle and use the clear supernatant. After removing the plate from the chromatographic chamber, allow it to dry in air or in a current of cool air and examine the chromatogram in ultraviolet light (254 nm).

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

A.2. Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance and applying 10 μ l of each of solutions (A) and (B). Examine the chromatogram in daylight.

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

B. The absorption spectrum of the final solution prepared for the Assay, when observed between 300 nm and 400 nm, exhibits one maximum at about 342 nm.

C. Shake a quantity of powdered tablets containing the equivalent of about 50 mg of amodiaquine with 20 ml of water and transfer to a separating funnel. Add 1 ml of ammonia (~260 g/l) TS and 25 ml of dichloromethane R and shake well. Let the layers separate and filter the dichloromethane extract through glass-fibre paper or a cotton plug previously washed and kept moistened with dichloromethane R. Evaporate the dichloromethane and dry the residue at 105°C for one hour. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from amodiaquine hydrochloride RS, treated in the same way as the test substance, or with the *reference spectrum* of amodiaquine.

D. To a quantity of powdered tablets containing the equivalent of about 0.15 g of amodiaquine add 10 ml of water R, shake well, and filter. The filtrate yields reaction B described under 2.1 General identification tests as characteristic of chlorides.

Related substances. Carry out the test as described under 1.14.1 Thin-layer chromatography. Prepare a solution of chloroform saturated with ammonia by shaking chloroform R with ammonia (~260 g/l) TS and separate the chloroform layer. Use silica gel R6 as the coating substance and a mixture of 9 volumes of chloroform saturated with ammonia, and 1 volume of dehydrated ethanol R as the mobile phase. Apply separately to the plate 10 μ l of each of the following two solutions in chloroform saturated with ammonia. For solution (1) shake a quantity of the powdered tablets containing the equivalent of 0.15 g amodiaquine with 10 ml vigorously for 2 minutes in a glass-stoppered test-tube, filter through a 0.45 filter and use the filtrate. For solution (2) dilute 1.0 ml of solution (1) to 200 ml. After removing the plate from the chromatographic chamber, allow it to dry in air or in a current of cool air and examine the chromatogram in ultraviolet light (254 nm).

Any spot obtained with solution (1), other than the principal spot, is not more intense than that obtained with solution (2).

Assay. Weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing the equivalent of about 0.3 g of amodiaquine, accurately weighed, to a 200 ml volumetric flask. Add about 150 ml of hydrochloric acid (~4 g/l) TS, sonicate for 15 minutes, allow to cool to room temperature, and make up to volume using the same solvent. Transfer 10.0 ml of the clear supernatant to a separating funnel. Add about 10 ml of hydrochloric acid (~4 g/l) TS, shake gently with 20 ml of chloroform R, let the layers separate well and discard the chloroform layer, retaining the aqueous layer quantitatively in the separating funnel. Add 5 ml of sodium hydroxide (~40 g/l) TS and extract with four 25 ml quantities of chloroform R. Combine the chloroform extracts and extract the resulting chloroform solution with three 50 ml quantities of hydrochloric acid (~4 g/l) TS. Combine the acid extracts and dilute to 200 ml with hydrochloric acid (~4 g/l) TS. Filter a portion of this solution through a 0.45 mm filter, discarding the first few ml of the filtrate. Dilute 20.0 ml of the clear filtrate to 100 ml with hydrochloric acid (~4 g/l) TS. Measure the absorbance of this solution in a 1 cm layer at the maximum at about 342 nm against a solvent cell containing hydrochloric acid (~4 g/l) TS. Calculate the content of amodiaquine, $C_{20}H_{22}ClN_3O$, using an absorptivity value of 47.8 ($A_{1\text{cm}}^{1\%} = 478$).

Reagents

Hydrochloric acid (~4 g/l) TS

Dilute 10 ml of hydrochloric acid (~420 g/l) TS with sufficient water to produce 1000 ml (approximately 0.1 mol/l)

Chloroquine sulfate oral solution

Draft proposal for the *International Pharmacopoeia* (June 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax +4122791 4730 or e-mail to rabhouansm@who.int

Category. Antimalarial.

Storage. Chloroquine sulfate oral solution should be kept in a well-closed container, protected from light.

Labelling. The designation of the container of Chloroquine sulfate oral solution should state that the active ingredient is in the sulfate form and the quantity should be indicated in terms of the equivalent amount of chloroquine.

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

50 mg of chloroquine is equivalent to approximately 68 mg of chloroquine sulfate.

REQUIREMENTS

Complies with the monograph for "Liquids for Oral Use".

Definition. Chloroquine sulfate oral solution is a solution of Chloroquine sulfate in a suitable flavoured vehicle. It contains not less than 90.0% and not more than 110.0% of the amount of chloroquine ($C_{18}H_{26}ClN_3$) stated on the label.

Identity tests

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

A.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 5 volumes of chloroform R, 4 volumes of cyclohexane R and 1 volume of diethylamine R as the mobile phase. Apply separately to the plate 2 μ l of each of the following two solutions. For solution (A) dilute a quantity of the oral solution containing the equivalent of 50 mg of chloroquine with 50 ml of water and add 4 ml of sodium hydroxide (~40 g/l) TS. Transfer to a separating funnel and extract with two 5 ml quantities of dichloromethane R. Use the combined dichloromethane extracts. For solution (B) use 6.8 mg chloroquine sulfate RS per ml water R. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or a current of cool air and examine the chromatogram in ultraviolet light (254 nm).

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

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Dip the plate in modified Dragendorff reagent TS. Examine the chromatogram in daylight.

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

B. The absorption spectrum of the final solution prepared for the Assay, when observed between 210 nm and 370 nm, exhibits maxima at about 220 nm, 235 nm, 256 nm, 329 nm and 342 nm.

C. To a quantity of the oral solution containing the equivalent of 50 mg of chloroquine add 10 ml of water and 1 ml of hydrochloric acid (~70 g/l) TS, and filter if necessary. To the filtrate add 1 ml of barium chloride (50 g/l) TS; a white precipitate is produced.

pH value. pH of the oral solution: 4.0 – 6.5.

Related substances. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 5 volumes of chloroform R, 4 volumes of cyclohexane R and 1 volume of diethylamine R as the mobile phase. Apply separately to the plate 2 μ l of each of the following three solutions. For solution (1) dilute a quantity of the oral solution containing the equivalent of

0.20 g of chloroquine with 50 ml of water and add 4 ml of sodium hydroxide (~40 g/l) TS. Transfer to a separating funnel and extract with two 5 ml quantities dichloromethane. Use the combined dichloromethane extracts. For solution (2) dilute 2 ml of solution (1) to 200 ml with dichloromethane. For solution (3) dilute 5 ml of solution (2) to 10 ml with dichloromethane. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or a current of cool air and examine the chromatogram in ultraviolet light (254 nm).

Any spot in the chromatogram obtained with solution (1), other than the principle spot, is not more intense than that in the chromatogram obtained with solution (2) (1.0%), and no more than one such spot is more intense than that obtained with solution (3) (0.5%).

[Note from the Secretariat: The related substances limits proposed above are in accordance with those in the BP monograph for Chloroquine Sulphate Oral Solution; the same limits are applied in the BP monograph for the tablets and for the API. The corresponding limits in the Ph.Int. monographs are 5% and 2.5% for Chloroquine sulfate tablets and a single limit of 2% for the API. It is suggested that the limits in the published Ph Int monographs should be reviewed.]

Assay. Dilute an accurately measured quantity of the oral solution containing the equivalent of 50 mg of chloroquine to 100 ml with water R. Dilute 2 ml to 100 ml with water. Filter a portion of this solution through a 0.45µm filter, discarding the first few ml of the filtrate. Measure the absorbance of the filtrate in a 1-cm layer at the maximum at about 342 nm against a solvent cell containing water R. Calculate the content of chloroquine, C₁₈H₂₆ClN₃, in the oral solution using an absorptivity value of 60.1 (A_{1cm}^{1%} = 601).

[Note from the Secretariat : A_{1cm}^{1%} value subject to confirmation.]

Paediatric artemether and lumefantrine oral suspension

Draft proposal for the *International Pharmacopoeia* (June 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41 22 791 4730 or e-mail to rabhouansm@who.int

Category. Antimalarial.

Storage. Paediatric artemether and lumefantrine powder for oral suspension should be kept in a well-closed container, protected from light.

Additional information. Not yet included in the current WHO Model List of Essential Medicines (EML). *EML Note:* "Not recommended in children below 5 kg".

REQUIREMENTS

Complies with the monograph for "Liquids for Oral Use"; the powder for oral suspension complies with the section of the monograph entitled "Powders and Granules for oral solutions and suspension" and with the requirements below.

Definition. Paediatric artemether and lumefantrine oral suspension is a suspension of Artemether and Lumefantrine in a suitable flavoured vehicle. It is prepared by suspending the powder for oral suspension in the specified volume of the liquid stated on the label.

The powder for oral suspension contains not less than 90.0% and not more than 110.0% of the amounts of artemether ($C_{16}H_{26}O_5$) and lumefantrine ($C_{30}H_{32}Cl_3NO$) stated on the label.

Identity tests

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

A.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 40 volumes of light petroleum R1, 10 volumes of ethyl acetate R and 5 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 μ l of each of the following 2 solutions in acetone R. For solution (A) shake a quantity of the powder for oral suspension equivalent to about 10 mg Artemether for 5 minutes with 10 ml, filter, and use the clear filtrate. For solution (B) use 1 mg artemether RS and a proportional quantity (according to the ratio in the powder for suspension) of lumefantrine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air.

(i) Examine the chromatogram in ultraviolet light (254 nm).

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

(ii) Spray the plate with sulfuric acid/methanol TS. Heat the plate for 10 minutes at 140°C. Examine the chromatogram in daylight.

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

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R5 as the coating substance and a mixture of 40 volumes of light petroleum R1, 10 volumes of ethyl acetate R and 5 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 μ l of each of the following 2 solutions in acetone R. For solution (A) shake a quantity of the powder for oral suspension equivalent to about 10 mg Artemether for 5 minutes with 10 ml, filter, and use the clear filtrate. For solution (B) use 1 mg artemether RS and a proportional quantity (according to the ratio in the powder for suspension) of lumefantrine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool

air. Spray with sulfuric acid/methanol TS. Heat the plate for 10 minutes at 140°C, allow it to cool and expose to iodine vapours for 20 minutes. Examine the chromatogram immediately in daylight.

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

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

Artemether-related substances

Protect samples from light, also during chromatography.

Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R5 as the coating substance and a mixture of 40 volumes of light petroleum R1, 10 volumes of ethyl acetate R and 5 volumes of glacial acetic acid R as the mobile phase.

Prepare the following solutions in the solvent consisting of 1 volume of purified water and 1 volume of acetonitrile R. For solution (1), shake a quantity of the powder for oral suspension containing 100 mg Artemether with a mixture of 100 ml water and 4 ml sodium hydroxide (~40 g/l) TS. Extract with four 15 ml quantities of dichloromethane R and evaporate the combined extracts to dryness. Add 10 ml of hexane R and evaporate to dryness. Sonicate the residue with 20 ml of the solvent for 15 minutes, centrifuge and use the clear supernatant. For solution (2) dissolve 2 mg of each of artemether RS, dihydroartemisinin (artemimol RS) and α -artemether RS in 20 ml of the solvent. For solution (3) dilute 2.0 ml of solution (2) to 20 ml with the solvent. For solution (4) dilute 3.0 ml of solution (2) to 20 ml with the solvent. For solution (5) dilute 5.0 ml of solution (2) to 20 ml with the solvent. For solution (6) dilute 1.0 ml of solution (2) to 2 ml with the solvent. For solution (7) dilute 3.0 ml of solution (2) to 4 ml with the solvent.

Apply separately to the plate 20 μ l of each of the solution (1), (3), (4), (5), (6) and (7). After application allow the spots to dry for 15 minutes in a current of cool air. Develop over a path of 12 cm. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool air. Dip the plate in sulfuric acid/methanol TS. Heat the plate for 10 minutes at 140°C. Examine the chromatogram in daylight.

Artemether and related substances have the following R_f values: impurity A about 0.25; dihydroartemisinin about 0.3; impurity B about 0.35; α -artemether about 0.4; artemether about 0.55.

In the chromatogram obtained with solution (1):

- any spot corresponding in R_f value to impurity A is not more intense than the spot corresponding to artemether obtained with solution (7) (1.5%),
- any spot corresponding in R_f value to dihydroartemisinin is not more intense than the spot corresponding to dihydroartemisinin obtained with solution (6) (1.0%),

- any spot corresponding in R_f value to impurity B is not more intense than the spot corresponding to artemether obtained with solution (5) (0.5%),
- any spot corresponding in R_f value to \acute{a} -artemether is not more intense than the spot corresponding to \acute{a} -artemether obtained with solution (4) (0.3%),
- the spot of any other impurity is not more intense than the spot corresponding to artemether obtained with solution (3) (0.2%). Disregard any spot remaining at the point of application.

Assay. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm x 3.9 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μ m) (Symmetry is suitable).

Use the following conditions for gradient elution:

Mobile phase A: 700 volumes of ion pair reagent and 300 volumes of acetonitrile R.

Mobile phase B: 300 volumes of ion pair reagent and 700 volumes of acetonitrile R.

Prepare the ion pair reagent by dissolving 5.65 g of sodium hexanesulfonate R and 2.75 g of sodium dihydrogen phosphate R in about 900 ml of purified water. Adjust the pH to 2.3 using phosphoric acid (~105 g/l) TS, dilute to 1000 ml and filter through a 0.45 μ m filter.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–28	60	40	Isocratic
28–29	60 to 0	40 to 100	Linear gradient
29–45	0	100	Isocratic
45–46	0 to 60	100 to 40	Linear gradient
46–55	60	40	Isocratic re-equilibration

Prepare the following solutions in the solvent which is obtained by mixing 200 ml of ion pair reagent, 60 ml of purified water and 200 ml of 1-propanol R and diluting to 1000 ml with acetonitrile R. For solution (1), transfer a quantity of the powder for oral suspension containing about 20 mg of Artemether, accurately weighed, to a 200 ml volumetric flask. Add 100 ml of the solvent, sonicate for 20 minutes, allow to cool to room temperature. Filter through a 0.45 μ m filter, discarding the first few ml of the filtered solution. For solution (2), accurately weigh 20 mg artemether RS and a proportional quantity (according to the ratio in the powder for suspension) of lumefantrine RS in a 100 ml volumetric flask. Add approximately 85 ml of solvent, sonicate until dissolved, allow to cool to room temperature and dilute to volume.

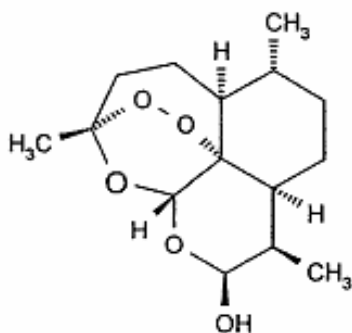
Operate with a flow rate of 1.3 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 210 nm for the first 28 minutes and then switch to about 380 nm.

Inject alternately 20 μ l each of solutions (1) and (2). (The peak for artemether is eluted at a retention time of approximately 19 minutes, and that for lumefantrine at a retention time of approximately 34 minutes.)

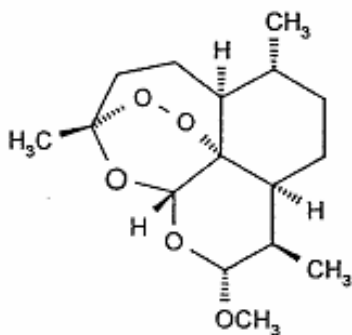
Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of artemether ($C_{16}H_{26}O_5$) and lumefantrine ($C_{30}H_{32}Cl_3NO$) in the powder for oral suspension.

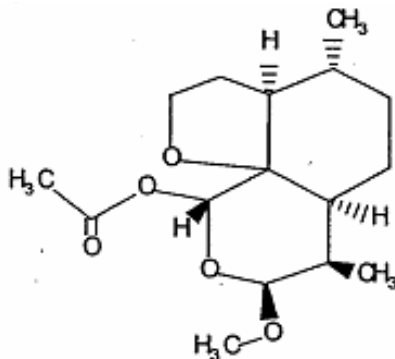
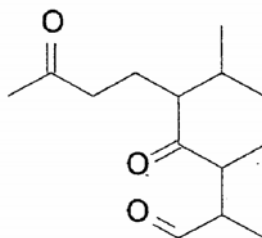
Impurities (artemether-related)

Dihydroartemisinin (artenimol) 284.4 $C_{15}H_{24}O_5$



α -artemether 298.4 $C_{16}H_{26}O_5$



B. 298.4 $C_{16}H_{26}O_5$ A. 298.3 $C_{16}H_{26}O_5$ 

[Names to be provided for A and B]

Sulfadoxine and pyrimethamine tablets

Draft proposal for the *International Pharmacopoeia* (June 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41 22 791 4730 or e-mail to rahhouansm@who.int

Category. Antimalarial.

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

Additional information. Strength in the current WHO Model list of essential medicines: 500 mg sulfadoxine and 25 mg pyrimethamine.

REQUIREMENTS

Comply with the monograph for "Tablets".

Definition. Sulfadoxine and Pyrimethamine tablets contain Sulfadoxine and Pyrimethamine. They contain not less than 90.0% and not more than 110.0% of the amounts of sulfadoxine ($C_{12}H_{14}N_4O_4S$) and pyrimethamine ($C_{12}H_{13}ClN_4$) stated on the label.

Identity tests

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

A.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 75 volumes of ethylacetate R, 25 volumes of methanol R and 1 volume of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 μ l of each of the following two solutions in methanol R. For solution (A) shake a quantity of the powdered tablets containing about 100 mg sulfadoxine for 5 minutes with 20 ml, filter, and use the filtrate. For solution (B) use 5 mg sulfadoxine RS and 0.25 mg pyrimethamine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in a current of air and examine the chromatogram in ultraviolet light (254 nm).

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

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Dip the plate in modified Dragendorff reagent TS. Examine the chromatogram in daylight.

The two principal spots obtained with solution A correspond in position, appearance, and intensity to those obtained with solution B (the spot for pyrimethamine is faintly visible).

B. See the test described below under Assay. The retention times of the two principal peaks in the chromatogram obtained with solution (1) are similar to those in the chromatogram obtained with solution (4).

Related Substances

[Note from Secretariat: The test for related substances is under investigation.]

Assay. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μ m) (Phenomenex is suitable).

As the mobile phase, use a solution prepared as follows: mix 200 volumes of acetonitrile R, 800 volumes of acetic acid (~10 g/l) TS and 0.5 volume of triethylamine R; adjust the pH to 4.2 by adding sodium hydroxide (~400 g/l) TS.

For solution (1) weigh and powder 20 tablets, and transfer a quantity of the powder containing about 0.50 g of Sulfadoxine, accurately weighed, into a 200 ml volumetric flask. Add about 70 ml of acetonitrile R and sonicate for 10 minutes. Allow to cool to room temperature, make up to volume using the mobile phase and sonicate for 10 minutes. Dilute 5 ml to 25 ml with mobile phase and filter a portion of this solution through a 0.45 μm filter, discarding the first few ml of the filtered solution. For solution (2), transfer 25 mg sulfadoxine RS, accurately weighed, to a 25ml volumetric flask, add about 10 ml acetonitrile R, sonicate until dissolved and dilute to volume with the mobile phase. For solution (3), transfer 25 mg pyrimethamine RS, accurately weighed, to a 25ml volumetric flask, add about 35 ml acetonitrile R, sonicate until dissolved and dilute to volume with the mobile phase. For solution (4) transfer 10 ml of solution (2) and 2 ml of solution (3) to a 20 ml volumetric flask and make up to volume with the mobile phase.

Operate with a flow rate of 2 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 254 nm.

Inject 20 μl of solution (4). The assay is not valid unless the resolution between the sulfadoxine and pyrimethamine peaks, eluting in this order, is at least 3. The run time for the analyses is not less than 25 min.

Inject alternately 20 μl each of solutions (1) and (4).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (4), and calculate the content of sulfadoxine, $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_4\text{S}$ and pyrimethamine, $\text{C}_{12}\text{H}_{13}\text{ClN}_4$ in the tablets.

Reagents

Acetic acid (~10 g/l) TS.

Acetic acid (~300 g/l) TS, diluted with water to contain about 10 g of $\text{C}_2\text{H}_4\text{O}_2$ per litre.

Quinine sulfate tablets

Draft proposal for the *International Pharmacopoeia* (June 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41 22 791 4730 or e-mail to rabhouansm@who.int

Category. Antimalarial.

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

Additional information. Strength in the current WHO Model list of essential medicines: 300 mg of quinine sulfate. The tablets are coated.

300 mg of quinine sulfate is equivalent to approximately 248.6 mg of anhydrous quinine.

REQUIREMENTS

Comply with the monograph for "Tablets".

Definition. Quinine sulfate tablets contain Quinine sulfate. They contain not less than 90.0% and not more than 110.0% of the amount of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2O_4S \cdot 2H_2O$ stated on the label.

Identity tests

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

A.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 20 volumes of toluene R, 12 volumes of ether R and 5 volumes of diethylamine R as the mobile phase. Apply separately to the plate 2 μ l of each of the following two solutions in a mixture of 2 volumes of chloroform R and 1 volume of ethanol (~750 g/l) TS. For solution (A) shake a quantity of the powdered tablets containing about 0.1 g Quinine sulfate with 10 ml, filter, and use the filtrate (if the tablets are sugar coated, the coating should be removed prior to powdering thereof). For solution (B) use 10 mg of quinine sulfate RS per ml and for solution (C) use 10 mg of quinine sulfate RS and 10 mg of quinidine sulfate RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in air or in a current of cool air and examine the chromatogram in ultraviolet light (254 nm).

The test is not valid unless the chromatogram obtained with solution C shows two clearly separated spots.

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

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Spray with sulfuric acid/ethanol (~0.05 mol/l) TS. and then with potassium iodobismuthate TS2. Examine the chromatogram in daylight.

The test is not valid unless the chromatogram obtained with solution C shows two clearly separated spots.

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

B. To a quantity of powdered tablets containing 50 mg of Quinine sulfate add 100 ml of water R, shake, and filter. To 10 ml of the filtrate add one drop of sulfuric acid (~100 g/l) TS. When examined in direct daylight or in ultraviolet light (366 nm) a strong blue fluorescence appears; it disappears almost completely on the addition of a few drops of hydrochloric acid (~70 g/l) TS.

C. To a quantity of powdered tablets containing 0.1 g of Quinine sulfate add 10 ml of water R, shake, and filter. The filtrate yields reaction A described under 2.1 General identification tests as characteristic of sulfates.

Related cinchona alkaloids. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R5 as the coating substance and a mixture of 20 volumes of toluene R, 12 volumes of ether R, and 5 volumes of diethylamine R as the mobile phase. Apply separately to the plate 4 μ l of each of the following four solutions in methanol R. For solution (1) sonicate a quantity of the powdered tablets containing 0.10 g Quinine sulfate with 10 ml for 10 minutes, filter, and use the filtrate (if the tablets are sugar coated, the coating should be removed prior to powdering thereof). For solution (2) use 0.31 mg of quinine sulphate R per ml and for solution (3) 0.25 mg of cinchonidine R per ml. For solution (4) dissolve 10 mg of quinine sulfate R in 1 ml of solution (3). After removing the plate from the chromatographic chamber, allow it to dry in a current of air for 15 minutes and repeat the development. Heat the plate at 105°C for 30 minutes, allow it to cool, spray it with potassium iodoplatinate TS, and examine the chromatogram in daylight.

The test is not valid unless the chromatogram obtained with solution (4) shows two clearly separated spots.

Any spot obtained with solution (1), other than the principal spot, is not more intense than that obtained with solution (2) or solution (3). Disregard any spot obtained with solution (1) immediately below the principal spot.

Dihydroquinine. Weigh and powder 20 tablets. Sonicate a quantity of the powder equivalent to about 0.20 g of Quinine sulfate, accurately weighed, in 20 ml of water R for 10 minutes. Add 0.5 g of potassium bromide R, 15 ml of hydrochloric acid (~70 g/l) TS and 0.1 ml of methyl red/ethanol TS. Titrate with potassium bromate (0.0167 mol/l) VS until a yellow colour is produced. Add 0.5 g of potassium iodide R in 200 ml of water, stopper the flask, and allow to stand in the dark for 5 minutes. Titrate the iodine liberated by excess potassium bromate in the solution with sodium thiosulfate (0.1 mol/l) VS, adding 2 ml of starch TS when the solution has reached a light yellow coloration. Each ml of potassium bromate (0.0167 mol/l) VS is equivalent to 26.10 mg of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$. Express the results of both the above determination and the assay in percentages, calculated with reference to the $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$. The difference between the two is not more than 10%.

Assay. Weigh and powder 20 tablets. Gently stir a quantity of the powder equivalent to about 0.40 g of Quinine sulfate, accurately weighed, in 40 ml of acetic acid R for 15 minutes. Titrate with perchloric acid (0.1 mol/l) VS, determine the end point potentiometrically as described under 2.6 Non-aqueous titration, Method A. Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 26.10 mg of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2O_4S_2 \cdot 2H_2O$.

Reagents

Sulfuric acid/ethanol (~0.05 mol/l)

Carefully add 4.9 g of sulfuric acid (~1760 g/l) TS to about 800 ml ethanol (~750 g/l) TS, while mixing gently, and dilute to 1000 ml with ethanol (~750 g/l) TS.

Rifampicin, isoniazid and ethambutol hydrochloride tablets

Draft proposal for the *International Pharmacopoeia* (June 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41 22 791 4730 or e-mail to rabhouansm@who.int

Category. Antituberculosis drugs.

Storage. Rifampicin, Isoniazid and Ethambutol hydrochloride tablets should be kept in a tightly closed container, protected from light.

Additional information. Strength in the current WHO Model list of essential medicines : 150 mg Rifampicin, 75 mg Isoniazid and 275 mg Ethambutol hydrochloride. The tablets are coated.

REQUIREMENTS

Comply with the monograph for "Tablets".

Definition. Rifampicin, Isoniazid and Ethambutol hydrochloride tablets contain Rifampicin, Isoniazid and Ethambutol Hydrochloride. They 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 ethambutol hydrochloride ($C_{10}H_{24}N_2O_2 \cdot 2HCl$) stated on the label.

Manufacture. The manufacturing process and the product packaging are designed and controlled so as to minimize the moisture content of the tablets. They ensure that, if tested, the tablets would comply with a loss on drying limit of not more than 30 mg/g when determined by drying freshly powdered tablets to constant mass under vacuum at 60 °.

Identity tests

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

A. See the test described below under Assay method A. The retention times of the two principal peaks in the chromatogram obtained with solution (1) correspond to those of the principal peaks in the chromatogram obtained with solution (2).

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

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

C.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 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 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 ultraviolet light (254 nm).

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

C.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Examine the chromatogram immediately in daylight.

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

Rifampicin-related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography, preparing the solutions and using the conditions given below under Assay method B.

Inject 20 µl each of solutions (1), (3) (4) and (5). The test is not valid unless in the chromatogram obtained with solution (4) the resolution between the peaks is at least 4.

In the chromatograms obtained with solutions (4) and (5) the following impurity peaks are eluted at the following relative retention with reference to rifampicin (retention time about 25 minutes): 3-(isonicotinoylhydrazinomethyl)rifamycin [the "hydrazone" resulting from reaction between 3-formylrifamycin and isoniazid] about 0.5; rifampicin quinone about 0.7.

In the chromatogram obtained with solution (1), the area of any peak corresponding to the hydrazone impurity is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (5.0%), the area of any peak corresponding to rifampicin quinone is not more than 0.8 times the area of the principal peak in the chromatogram obtained with solution (3) (4.0%) and the area of any other peak is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (3) (1.5%). The sum of the areas of all the peaks, other than the principal peak, is not greater than twice the area of the principal peak obtained with solution (3) (10.0% with reference to the content of rifampicin). Disregard any peak with an area less than 0.02 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%) and any peak with relative retention time less than 0.23 with reference to rifampicin.

[Note from the Secretariat: As agreed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations for the finalized texts for TB dosage form monographs published on the Medicines web site (QSM/EC/06.13), solution (5) (see under Assay method B) describes the *in situ* preparation of the hydrazone impurity. The agreed change will be made to the finalized texts before inclusion in the first Supplement to the 4th edition.]

Assay

A. For isoniazid and ethambutol hydrochloride

Determine by 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups, (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 with glacial acetic acid R. Mix 940 ml of this solution with 60 ml methanol R.

Prepare the following solutions in water. For solution (1) 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. [If foaming occurs, use 400 ml of a 4% solution of methanol R in place of the water.] 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 (2) dissolve 27.3 mg of isoniazid 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 alternately 20 µl each of solutions (1) and (2). (The peak for isoniazid is eluted at a retention time of approximately 1.6 minutes, and that for ethambutol hydrochloride at a retention time of approximately 6 minutes.)

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of isoniazid, C₆H₇N₃O and ethambutol hydrochloride, C₁₀H₂₄N₂O₂, 2HCl.

B. For rifampicin

Prepare fresh solutions and perform the assay without delay. Low-actinic glassware is recommended.

Determine by 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups, (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 R (0.01 mol/l), adjusted with sodium hydroxide (0.1 mol/l)VS).

Prepare the following solutions in a mixture of 4 volumes of methanol R and 6 volumes of phosphate buffer pH 7.0. For solution (1) weigh and powder 20 tablets. Without delay, shake a quantity of the powder equivalent to about 40 mg Rifampicin in 200 ml and filter. Solution (2) contains 0.20 mg rifampicin RS per ml. For solution (3) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 10 µg Rifampicin per ml. Solution (4) contains 0.2 mg rifampicin RS per ml and 0.2 mg rifampicin quinone RS per ml. For solution (5) dissolve 4 mg of rifampicin RS and 2 mg of isoniazid RS in 25.0 ml of acetic acid (~60g/l) TS and keep the solution at room temperature 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 about 254 nm.

Inject 20 µl of solution (4). The assay is not valid unless the resolution between the peaks is at least 4.

Inject alternately 20 µl each of solutions (1) and (2). Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of rifampicin, $C_{43}H_{58}N_4O_{12}$ in the tablets.

[Note from the Secretariat: The preparation of solutions (1) to (4) has been modified from that described in the finalized texts for TB dosage form monographs published on the Medicines website in order to improve the stability of the test solution. It is intended to make corresponding changes to the finalized texts before inclusion in the first Supplement to the 4th edition.]

Dissolution test. *To be added for rifampicin.*

Rifampicin and Isoniazid dispersible tablets

Draft proposal for the *International Pharmacopoeia* (June 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41 22 791 4730 or e-mail to rabhouansm@who.int

Category. Antituberculosis drugs.

Storage. Rifampicin and Isoniazid dispersible tablets should be kept in a tightly closed container, protected from light.

Additional information. [Dispersible tablets are not included in the current WHO Model List of Essential Medicines. It is understood that the following strengths are available as dispersible tablets: 60 mg Rifampicin and 30 mg Isoniazid, 60 mg Rifampicin and 60 mg Isoniazid.]

REQUIREMENTS

Comply with the monograph for "Tablets".

Definition. Rifampicin and Isoniazid dispersible tablets contain Rifampicin and Isoniazid in a suitable dispersible basis that may contain suitable flavouring agents. They 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 tests A and B or test C may be applied.

A. See Assay method A described below. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

B. See Assay method B described below. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

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

C.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 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 containing about 5 mg Isoniazid for 15 minutes with 5 ml, 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. After removing the plate from the chromatographic chamber, allow it to dry in a current of air and examine the chromatogram in ultraviolet light (254 nm).

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

C.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Examine the chromatogram immediately in daylight. Add detection by iodine vapour...

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

Disintegration. Disintegrate within 3 minutes when examined by 5.3 Disintegration test for tablets and capsules, but using water R at 15 to 25 °C.

Dissolution test. [To be added for rifampicin.]

Rifampicin-related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given below under Assay method B.

Inject alternately 20 µl each of solutions (1), (3), (4) and (5). The test is not valid unless in the chromatogram obtained with solution (4) the resolution between the peaks is at least 4.

In the chromatograms obtained with solutions (4) and (5) the following impurity peaks are eluted at the following relative retention with reference to rifampicin (retention time about 25 minutes): 3-(isonicotinoylhydrazinomethyl)rifampicin [the "hydrazone" resulting from reaction between 3-formylrifampicin and isoniazid] about 0.5; rifampicin quinone about 0.7.

In the chromatogram obtained with solution (1), the area of any peak corresponding to the hydrazone impurity is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (5.0%), the area of any peak corresponding to rifampicin quinone is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (3) (4.0 %) and the area of any other peak is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (3) (1.5%). The sum of the areas of all the peaks, other than the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (10.0%). Disregard any peak with an area less than 0.02 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%) and any peak with a relative retention less than 0.23 with reference to rifampicin.

Assay

A. **For isoniazid.** Determine by 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (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 with glacial acetic acid R. Mix 940 ml of this solution with 60 ml methanol R.

Prepare the following solutions in water. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powder containing about 30 mg Isoniazid, accurately weighed, to a 500 ml volumetric flask. Dissolve in about 400 ml water by shaking for about 15 minutes. [If foaming occurs, use 400 ml of a 4% solution of methanol R in place of the water.] 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 (2) 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 alternately 20 μl each of solutions (1) and (2). The peak for isoniazid is eluted at a retention time of about 1.6 minutes.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of isoniazid, $\text{C}_6\text{H}_7\text{N}_3\text{O}$, in the tablets.

B. **For rifampicin.** Prepare fresh solutions and perform the assay without delay. Low-actinic glassware is recommended.

Determine by 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (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 R (0.01 mol/l), adjusted with sodium hydroxide (0.1 mol/l) VS).

Prepare the following solutions in a mixture of 4 volumes of methanol R and 6 volumes of phosphate buffer pH 7.0. For solution (1) weigh and powder 20 tablets. Without delay, shake a quantity of the powder containing about 40 mg Rifampicin in

200 ml and filter. Solution (2) contains 0.20 mg rifampicin RS per ml. For solution (3) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 10 µg Rifampicin per ml. Solution (4) contains 0.2 mg rifampicin RS per ml and 0.2 mg rifampicin quinone RS per ml. For solution (5) dissolve 4 mg of rifampicin RS and 2 mg of isoniazid RS in 25 ml of acetic acid (~60 g/l) TS and keep the solution at room temperature 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 about 254 nm.

Inject 20 µl of solution (4). The assay is not valid unless the resolution between the peaks is at least 4.

Inject alternately 20 µl each of solutions (1) and (2). Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of rifampicin, $C_{43}H_{58}N_4O_{12}$, in the tablets.

Rifampicin, isoniazid and pyrazinamide dispersible tablets

Draft proposal for the *International Pharmacopoeia* (June 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41 22 791 4730 or e-mail to rrahhouansm@who.int

Category. Antituberculosis drugs.

Storage. Rifampicin, Isoniazid and Pyrazinamide dispersible tablets should be kept in a tightly closed container, protected from light.

Additional information. Not included in the current WHO Model List of Essential Medicines. It is understood that the following strengths are available as dispersible tablets: 60 mg Rifampicin, 30 mg Isoniazid and 150 mg Pyrazinamide.

REQUIREMENTS

Comply with the monograph for "Tablets".

Definition. Rifampicin, Isoniazid and Pyrazinamide dispersible tablets contain Rifampicin, Isoniazid and Pyrazinamide in a suitable dispersible basis that may contain suitable flavouring agents. They 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 tests A and B or test C may be applied.

A. See Assay method A described below. The retention times of the two principal peaks in the chromatogram obtained with solution (1) correspond to those of the principal peaks in the chromatogram obtained with solution (2).

B. See Assay method B described below. The retention time of the principal peak in

the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

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

C.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 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 containing about 5 mg Isoniazid for 15 minutes with 5 ml, 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. After removing the plate from the chromatographic chamber, allow it to dry in a current of air and examine the chromatogram in ultraviolet light (254 nm).

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

C.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Examine the chromatogram immediately in daylight.

Add detection by iodine vapour...

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

Disintegration. Disintegrate within 3 minutes when examined by 5.3 Disintegration test for tablets and capsules, but using water R at 15-25 °C.

Dissolution test. [To be added for rifampicin.]

Rifampicin-related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given below under Assay method B.

Inject alternately 20 µl each of solutions (1), (3), (4) and (5). The test is not valid unless in the chromatogram obtained with solution (4) the resolution between the peaks is at least 4.

In the chromatograms obtained with solutions (4) and (5) the following impurity peaks are eluted at the following relative retention with reference to rifampicin (retention time about 25 minutes): 3-(isonicotinoylhydrazinomethyl)rifamycin [the "hydrazone" resulting from reaction between 3-formylrifamycin and isoniazid] about 0.5; rifampicin quinone about 0.7.

In the chromatogram obtained with solution (1), the area of any peak corresponding to the hydrazone impurity is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (5.0%), the area of any peak corresponding to rifampicin quinone is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (3) (4.0 %) and the area of any other peak is not greater than 0.3 times the area of the principal peak in the chromatogram obtained

with solution (3) (1.5%). The sum of the areas of all the peaks, other than the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (10.0%). Disregard any peak with an area less than 0.02 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%) and any peak with a relative retention less than 0.23 with reference to rifampicin.

Assay

A. For isoniazid and pyrazinamide. Determine by 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (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 with glacial acetic acid R. Mix 940 ml of this solution with 60 ml methanol R.

Prepare the following solutions in water. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powder containing about 30 mg Isoniazid, accurately weighed, to a 500 ml volumetric flask. Dissolve in about 400 ml water by shaking for about 15 minutes. [If foaming occurs, use 400 ml of a 4% solution of methanol R in place of the water.] 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 (2) 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 (2). The assay is not valid unless the resolution between the isoniazid and pyrazinamide peaks, eluting in this order, is at least 2.

Inject alternately 20 µl each of solutions (1) and (2). Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of isoniazid, C₆H₇N₃O, and pyrazinamide, C₅H₅N₃O, in the tablets.

B. For rifampicin. Prepare fresh solutions and perform the assay without delay. Low-actinic glassware is recommended.

Determine by 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (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 R (0.01 mol/l), adjusted with sodium hydroxide (0.1 mol/l)VS).

Prepare the following solutions in a mixture of 4 volumes of methanol R and 6 volumes of phosphate buffer pH 7.0. For solution (1) weigh and powder 20 tablets. Without delay, shake a quantity of the powder containing about 40 mg Rifampicin in 200 ml and filter. Solution (2) contains 0.20 mg rifampicin RS per ml. For solution (3) dilute a

suitable volume of solution (1) to obtain a concentration equivalent to 10 µg Rifampicin per ml. Solution (4) contains 0.2 mg rifampicin RS per ml and 0.2 mg rifampicin quinone RS per ml. For solution (5) dissolve 4 mg of rifampicin RS and 2 mg of isoniazid RS in 25 ml of acetic acid (~60 g/l) TS and keep the solution at room temperature 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 about 254 nm.

Inject 20 µl of solution (4). The assay is not valid unless the resolution between the peaks is at least 4.

Inject alternately 20 µl each of solutions (1) and (2). Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of rifampicin, $C_{43}H_{58}N_4O_{12}$, in the tablets.

Efavirenz capsules

Draft proposal for the *International Pharmacopoeia* (May 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41 22 791 4730 or e-mail to rabhouansm@who.int

Category. Antiretroviral (Non-nucleoside Reverse Transcriptase Inhibitor).

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

Additional information. Strength in the current WHO Model List of Essential Medicines: 50 mg

REQUIREMENTS

Comply with the monograph for "Capsules".

Definition. Efavirenz capsules contain Efavirenz. They contain not less than 90.0% and not more than 110.0% of the amount of $C_{14}H_9ClF_3NO_2$ stated on the label.

Identity tests

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

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

A.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 90 volumes of dichloromethane R, 10 volumes of methanol R and 3 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 5 µl of each of 2 solutions in methanol R containing (A) shake a quantity of the content of the capsules containing 5 mg of Efavirenz

with 5 ml, filter and use the clear filtrate and (B) 1 mg of efavirenz RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool 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 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Spray the plate with 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. See the test described below under Assay method A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

C. The absorption spectrum of the final solution prepared for Assay method B, when observed between 210 nm and 300 nm, exhibits one maximum at about 247 nm.

D. To a quantity of the contents of the capsules containing 25 mg of Efavirenz, add 10 ml of methanol R, shake to dissolve and filter. Evaporate the filter to dryness. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from efavirenz RS or with the *reference spectrum* of efavirenz.

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

Related substances

Note: Prepare fresh solutions and perform the test without delay.

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Assay method A.

Prepare the following solutions in a mixture of 50% acetonitrile R and 50% water R (dissolution solvent). For solution (1) transfer a quantity of the content of the capsules containing 25 mg of Efavirenz into the dissolution solvent and dilute to 25.0 ml with the same solvent. For solution (2) dilute 1.0 ml of solution (1) to 50.0 ml with the dissolution solvent and dilute 5.0 ml of the resulting solution to 100.0 ml with the same solvent. For solution (3) dissolve about 5 mg of efavirenz for system suitability RS (containing efavirenz and impurities A to F) in 5 ml of the dissolution solvent.

Inject separately 35 µl of each solution (1), (2) and (3) and of the dissolution solvent in the chromatographic system. Examine the blank chromatogram for any extraneous

peaks and disregard the corresponding peaks observed in the chromatogram obtained with solution (1).

In the chromatogram obtained with solution (3), the impurity B peak is eluted at a relative retention of about 0.9 with reference to efavirenz (retention time about 20 minutes). The test is not valid unless the resolution factor between the peaks due to impurity B and efavirenz is at least 3.

In the chromatogram obtained with solution (1) the area of any peak corresponding to impurity B is not greater than four times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%), the area of any other peak, apart from the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%) and the area of not more than three such peaks is greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%). The sum of the areas of all peaks, other than the principal peak, is not greater than 8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%). 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

Either method A or method B may be applied.

A. Carry out the assay as described under 1.14.4 High-performance liquid Chromatography using a stainless steel column (15 cm x 4.6 mm, 3.5 μ m), packed with cyanopropylidimethylsilane monolayer (Zorbax[®] SB-CN is suitable).

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

Mobile phase A: 90 vol of a 0.05% solution of trifluoroacetic acid R and 10 vol of methanol R.
 Mobile phase B: 10 vol of a 0.05% solution of trifluoroacetic acid R and 90 vol of methanol R.

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0	60	40
16	50	50
23	35	65
28	30	70
29	20	80
31	20	80
32	60	40
40	60	40

Prepare the following solutions in a mixture of 50% acetonitrile R and 50% water R (dissolution solvent). For solution (1) mix the content of 20 capsules and transfer a quantity containing about 25 mg of Efavirenz, accurately weighed, into the dissolution

solvent and dilute to 25.0 ml with the same solvent. Dilute 1.0 ml of the resulting solution to 100.0 ml with the dissolution solvent. For solution (2) dissolve 25 mg of efavirenz RS in the dissolution solvent and dilute to 25.0 ml with the same solvent. Dilute 1.0 ml of the resulting solution to 100.0 ml with the dissolution solvent. For solution (3) dissolve about 5 mg of efavirenz for system suitability RS (containing efavirenz and impurities A to F) in 5 ml of the dissolution solvent.

Operate with a flow rate of 1.5 ml per minute. as a detector use an ultraviolet spectrophotometer set at a wavelength of about 250 nm.

Inject separately 35 µl of solutions (1), (2) and (3). In the chromatogram obtained with solution (3), the impurity B peak is eluted at a relative retention of about 0.9 with reference to efavirenz (retention time about 20 minutes). The assay is not valid unless the resolution factor between the peaks due to impurity B and efavirenz is at least 3.

Measure the areas of the peaks responses obtained in the chromatogram from solutions (1) and (2), and calculate the content of $C_{14}H_9ClF_3NO_2$ in the capsules.

B. Mix the content of 20 capsules and transfer a quantity containing about 25 mg of Efavirenz, accurately weighed, to a 50.0 ml volumetric flask. Add about 25 ml of methanol R, sonicate for about 5 minutes, allow to cool to room temperature and make up the volume using the same solvent. Filter a portion of this solution through a 0.45 µm filter, discarding the first few ml of the filtrate. Dilute 1.0 of this solution to 50.0 ml with the same solvent. Measure the absorbance (1.6) of 1-cm layer of the diluted solution at the maximum at about 247 nm. Calculate the amount of $C_{14}H_9ClF_3NO_2$ in the capsules using an absorptivity value of 47.3 (specific absorbance $A_{1\text{cm}}^{1\%} = 473$).

Impurities. The impurities limited by the requirements of this monograph include those listed in the monograph for Efavirenz.

Nevirapine oral solution

Draft proposal for the *International Pharmacopoeia* (April 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41 22 791 4730 or e-mail to rabhouansm@who.int

Category. Antiretroviral

Storage. Nevirapine oral solution should be kept in a well-closed container,

Labelling. The designation of the container of nevirapine oral solution should state that the active ingredient is the hemihydrate form and the quantity should be indicated in terms of the equivalent amount of nevirapine.

Additional information. Strength in the current WHO Model List of Essential Medicines: 50 mg/5 ml.

REQUIREMENTS

Complies with the monograph for "Liquids for oral use".

Definition. Nevirapine oral suspension contains Nevirapine as the hemihydrate. It contains not less than 90.0% and not more than 110.0% of the amount of $C_{15}H_{14}N_4O$ stated on the label.

Identity tests

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

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

A.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 90 volumes of dichloromethane R, 10 volumes of methanol R and 3 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 5 μ l of each of 2 solutions in methanol: (A) transfer an accurately measured volume of the oral suspension equivalent to 5 mg of nevirapine with 5 ml and (B) 1 mg of anhydrous nevirapine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool 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 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Spray the plate with 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. See the test described below under Assay. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that obtained with solution (2).

C. To a volume of the oral suspension equivalent to about 100 mg of nevirapine add 8 ml methanol R, shake and filter. The absorption spectrum, when observed between 220 nm and 350 nm, exhibits a maximum at about 283 nm.

Related substances

Note: Prepare fresh solutions and perform the tests without delay

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Assay.

Prepare the following solutions. For solution (1) transfer a volume of the oral suspension equivalent to about 24 mg of nevirapine in 4 ml of acetonitrile R, add 80 ml of the

mobile phase and sonicate. Dilute to 100.0 ml with the mobile phase. For solution (2) dilute 5.0 ml of solution (1) to 50.0 ml with the mobile phase. Dilute 5.0 ml of the resulting solution to 50.0 ml with the same solvent. For solution (3) dissolve 6 mg of nevirapine impurity B RS in a mixture of 25 ml of acetonitrile R and 55 ml of mobile phase, sonicate for 15 min and dilute to 100.0 ml with the mobile phase. Mix 6.0 ml of the resulting solution with 3.0 ml of solution (1) and dilute to 50.0 ml with the mobile phase.

Inject separately 50 μ l each of solutions (1), (2) and (3) and of mobile phase in the chromatographic system and record the chromatograms for 9 times the retention time of nevirapine. Examine the mobile phase chromatogram for any extraneous peaks and disregard the corresponding peaks observed in the chromatogram obtained with solution (1).

In the chromatogram obtained with solution (3), the following impurity peaks are eluted at the following retention ratios with reference to nevirapine (retention time = about 7.6 min): impurity B = about 0.7; impurity A = about 1.5; impurity C = about 2.8. The test is not valid unless the resolution factor between the peaks due to nevirapine and nevirapine impurity B is at least 5.

In the chromatogram obtained with solution (1) the area of any individual peak corresponding to impurity A or C is not greater than 0.2 times the area of the principal peak obtained with solution (2) (0.2%) and 0.77 times the area of any individual peak corresponding to impurity B is not greater than 0.2 times the area of the principal peak obtained with solution (2) (0.2%). The area of any other impurity peak is not greater than 0.1 times the area of the principal peak obtained with solution (2) (0.1%). The sum of the areas of all peaks, other than the principal peak, is not greater than 0.6 times the area of the principal peak obtained with solution (2) (0.6%). Disregard any peak with an area less than 0.05 times the area of the principal peak obtained with solution (2) (0.05%)

Assay. Carry out the assay as described under 1.14.4 High-performance liquid Chromatography using a stainless steel column (15 cm x 4.6 mm), packed with particles of silica gel, the surface of which has been modified with chemically bonded hexadecylamidylsilyl groups (5 μ m) (Supelcosil LC-ABZ is suitable).

Maintain the column temperature at 35 °C.

The mobile phase consists of a filtered and degassed mixture of 20 volumes of acetonitrile R and 80 volumes of a 3.6 g/l solution of ammonium dihydrogen phosphate R adjusted to pH 5.0 using ammonia (~260 g/l) TS.

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

Prepare the following solutions. For solution (1) transfer an accurately weighed volume of the oral suspension equivalent to about 24 mg of nevirapine in 4 ml of acetonitrile R, add 80 ml of the mobile phase and sonicate. Dilute to 100.0 ml with the mobile phase (solution A). Dilute 3.0 ml of solution A to 50.0 ml with the mobile phase. For solution (2) dissolve 12 mg of anhydrous nevirapine RS in 2 ml of acetonitrile R and 40 ml of

the mobile phase and sonicate. Dilute to 50.0 ml with the mobile phase and dilute 3.0 ml of the resulting solution to 50.0 ml with the mobile phase. For solution (3) dissolve 6 mg of nevirapine impurity B RS in a mixture of 25 ml of acetonitrile R and 55 ml of mobile phase, sonicate for 15 min and dilute to 100.0 ml with the mobile phase. Mix 6.0 ml of the resulting solution with 3.0 ml of solution A and dilute to 50.0 ml with the mobile phase.

Inject separately 50 μ l of solutions (1), (2) and (3). In the chromatogram obtained with solution (3), the impurity B peak is eluted at a relative retention of about 0.7 with reference to nevirapine (retention time about 7.6 minutes). The assay is not valid unless the resolution between nevirapine and nevirapine impurity B is at least 5.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). Determine the weight per ml (1.3.1) of the oral suspension and calculate the content of $C_{15}H_{14}N_4O$, weight in volume, in the oral suspension.

[*Note from the Secretariat:* method text 1.3.1 attached for information.]

Impurities. The impurities limited by the requirements of this monograph include those listed in the monograph for Nevirapine.

Nevirapine tablets

Draft proposal for the *International Pharmacopoeia* (April 2007). Please address any comments to Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Fax +41 22 791 4730 or e-mail to rabhouansm@who.int

Category. Antiretroviral

Storage. Nevirapine tablets should be kept in a well-closed container,

Labelling. The designation of the container of nevirapine tablets should state that the active ingredient is the anhydrous form.

Additional information. Strength in the current WHO Model List of Essential Medicines: 200 mg

REQUIREMENTS

Comply with the monograph for "Tablets".

Definition. Nevirapine tablets contain Nevirapine in the anhydrous form. They contain not less than 90.0% and not more than 110.0% of the amount of $C_{15}H_{14}N_4O$ stated on the label.

Identity tests

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

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

A.1. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 90 volumes of dichloromethane R, 10 volumes of methanol R and 3 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 5 μ l of each of 2 solutions in methanol R: (A) shake a quantity of the powdered tablets containing 5 mg of nevirapine with 5 ml, filter and use the clear filtrate and (B) 1 mg of anhydrous nevirapine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of cool 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 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Spray the plate with 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 the final solution prepared for the assay, when observed between 220 nm and 350 nm, exhibits a maximum at about 283 nm.

C. To a quantity of the powdered tablets containing 50 mg of nevirapine add 10 ml of methanol R, shake to dissolve and filter, Evaporate the filtrate to dryness. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from anhydrous nevirapine RS or with the *reference spectrum* of anhydrous nevirapine.

Related substances

Note: Prepare fresh solutions and perform the tests without delay

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Assay.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets and transfer a quantity of the powder equivalent to about 24 mg of nevirapine in 4 ml of acetonitrile R, add 80 ml of the mobile phase and sonicate. Dilute to 100.0 ml with the mobile phase and filter if necessary. For solution (2) dilute 5.0 ml of solution (1) to 50.0 ml with the mobile phase. Then dilute 5.0 ml of this solution to 50.0 ml with the same solvent. For solution (3) dissolve 6 mg of nevirapine impurity B RS in a mixture of 25 ml of acetonitrile R and 55 ml of mobile phase, sonicate for 15 min and dilute to 100.0 ml with the mobile phase. Then mix 6.0 ml of this solution with 3.0 ml of solution (1) and dilute to 50.0 ml with the mobile phase.

Inject separately 50 μ l each of solution (1) (2) and (3) and of mobile phase in the chromatographic system and record the chromatograms for 6 times the retention time of nevirapine. Examine the mobile phase chromatogram for any extraneous peaks

and disregard the corresponding peaks observed in the chromatogram obtained with solution (1).

In the chromatogram obtained with solution (3), the following impurity peaks are eluted at the following retention ratios with reference to nevirapine (retention time = about 7.6 min): impurity B = about 0.7; impurity A = about 1.5; impurity C = about 2.8. The test is not valid unless the resolution factor between the peaks due to nevirapine and nevirapine impurity B is at least than 5.

In the chromatogram obtained with solution (1) the area of any individual peak corresponding to impurity A or C is not greater than 0.2 times the area of the principal peak obtained with solution (2) (0.2%) and 0.77 times the area of any individual peak corresponding to impurity B is not greater than 0.2 times the area of the principal peak obtained with solution (2) (0.2%). The area of any other impurity peak is not greater than 0.1 times the area of the principal peak obtained with solution (2) (0.1%). The sum of the areas of all peaks, other than the principal peak, is not greater than 0.6 times the area of the principal peak obtained with solution (2) (0.6%). Disregard any peak with an area less than 0.05 times the area of the principal peak obtained with solution (2) (0.05%)

Assay

Either method A or method B may be applied.

A. Carry out the assay as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm x 4.6 mm), packed with particles of silica gel, the surface of which has been modified with chemically bonded hexadecylamidylysilyl groups (5 μ m) (Supelcosil LC-ABZ is suitable).

Maintain the column temperature at 35°C.

The mobile phase consists of a filtered and degassed mixture of 20 volumes of acetonitrile R and 80 volumes of a 3.6 g/l solution of ammonium dihydrogen phosphate R adjusted to pH 5.0 using ammonia (~260 g/l) TS.

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

Prepare the following solutions. For solution (1) weigh and powder 20 tablets and transfer a quantity of the powder equivalent to about 24 mg of nevirapine, accurately weighed, in 4 ml of acetonitrile R, add 80 ml of the mobile phase and sonicate. Dilute to 100.0 ml with the mobile phase and filter if necessary (solution A). Dilute 3.0 ml of solution A to 50.0 ml with the mobile phase. For solution (2) dissolve 12 mg of anhydrous nevirapine RS in 2 ml of acetonitrile R and 40 ml of the mobile phase and sonicate. Dilute to 50.0 ml with the mobile phase and dilute 3.0 ml of the resulting solution to 50.0 ml with the mobile phase. For solution (3) dissolve 6 mg of nevirapine impurity B RS in a mixture of 25 ml of acetonitrile R and 55 ml of mobile phase, sonicate for 15 min and dilute to 100.0 ml with the mobile phase. Mix 6.0 ml of this solution with 3.0 ml of solution A and dilute to 50.0 ml with the mobile phase.

Inject separately 50 μ l of solutions (1), (2) and (3). In the chromatogram obtained with solution (3), the impurity B peak is eluted at a relative retention of about 0.7 with reference to nevirapine (retention time about 7.6 minutes). The assay is not valid unless the resolution factor between the peaks due to nevirapine and nevirapine impurity B is at least 5.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of $C_{15}H_{14}N_4O$ in the tablets.

B. Weigh and powder 20 tablets. Transfer a quantity of the powder containing about 20 mg of nevirapine, accurately weighed, to a 100 ml volumetric flask. Add about 25 ml of methanol R, sonicate for about 5 minutes, allow to cool to room temperature, and make up the volume using the same solvent. Filter a portion of this solution through a 0.45 μ m filter, discarding the first few ml of the filtrate. Dilute 5.0 ml of the filtrate to 100.0 ml with the same solvent. Measure the absorbance of this solution in a 1 cm layer at the maximum at about 283 nm against a solvent cell containing methanol R.

Calculate the content of $C_{15}H_{14}N_4O$ in the tablets using an absorptivity value of 26.7 ($A_{1\text{cm}}^{1\%} = 267$).

Impurities. The impurities limited by the requirements of this monograph include those listed in the monograph for Nevirapine.

Recent Publications, Information and Events

Pharmacogenomics guidance from Health Canada

Health Canada has released *Submission of Pharmacogenomic Information*, the final version of a regulatory guidance document issued following public consultation in 2006. It provides guidance to sponsors on how and when to submit pharmacogenomic information to Health Canada.

The document was prepared for sponsors intending to submit pharmacogenomic information to Health Canada in support of an application or submission for a drug, biologic drug, or pharmacogenomic test at the clinical trial and new drug submission stages. The document contains policy statements and regulatory guidance on the following topics:

- clinical trials and new drug submissions involving pharmacogenomic tests;
- pharmacogenomic testing for exploratory research purposes;
- informed consent for pharmacogenomic testing; and
- labelling considerations.

The document also provides guidance on the submission of pharmacogenomic information as part of ongoing postmarketing activities.

Pharmacogenomics is an evolving field and this guidance document is intended to promote dialogue between sponsors and regulators on submissions containing pharmacogenomic information or data supporting the development of a therapeutic agent. As opposed to other agencies such as the US Food and Drug

Administration (FDA) and the European Medicines Evaluation Agency (EMA), Health Canada is not requesting sponsors to submit voluntary genomic data. Instead, they are encouraged to request pre-submission consultation meetings prior to filing pharmacogenomic applications or submissions.

Additionally, the International Conference on Harmonization (ICH) is in the final stages of developing a Guideline on Pharmacogenomic Terminology (Topic E15). Health Canada intends to update its guidance document over time to incorporate ICH terminology and to reflect experience gained. As an active observer and contributor to the E15 Expert Working Group, Health Canada is committed to adopting ICH guidelines and to continue contributing to ICH harmonization efforts.

Reference: http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/pharmaco/index_e.html

Untangling the web: tenth edition

Untangling the web of price reductions is a pricing guide for the purchase of antiretroviral medicines for developing countries, prepared by the Medecins Sans Frontieres Campaign for Access to Essential Medicines. The publication provides information in simple table format about the prices and suppliers of antiretroviral drugs in developing countries.

The prices listed are selling prices as quoted from the manufacturers. In addition, the guide provides information about where the particular price offers by

pharmaceutical companies are valid, what type of treatment provider is eligible for them as well as other conditions linked to the offers.

Similarly, as a pricing guide it does not include information about the quality of the products listed. Price should not be the only factor determining procurement decisions.

Reference: <http://www.accessmed-msf.org/documents/Untangling10.pdf> or from Fernando.pascual@geneva.msf.org

Priorities for dengue control

Dengue is the most rapidly spreading vector borne disease. An estimated 50 million



dengue infections occur annually and approximately 2.5 billion people live in dengue endemic countries. Because of the rapidly increasing public health importance of this disease, in 1999 dengue was incorporated in the portfolio of the UNICEF, UNDP,

World Bank, WHO Special Programme for Research and Training in Tropical Diseases (TDR). The 2002 World Health Assembly Resolution WHA55.17 urged greater commitment to dengue among Member States and WHO; of particular significance is the 2005 Revision of the International Health Regulations (WHA58.3), which includes dengue as an example of a disease that may constitute a public health emergency of international concern.

It was against this background that the Dengue Scientific Working Group of 60 experts from 20 countries including WHO

staff from four Regions and Headquarters met in Geneva in October 2006 to review existing knowledge and establish priorities for future research aimed at improving dengue treatment, prevention and control.

Reference: Scientific working group on dengue. TDR/SWG/08-2007 available at Bookorders@who.int

PLoS Neglected Tropical Diseases open access journal

The Public Library of Science, PLoS, is announcing a new open-access online journal, PLoS Neglected Tropical Diseases at <http://www.plosntds.org>

All PLoS articles are freely available online to use and share, and the copyright remains with the author.

This new journal will focus on the scientific, medical and public-health aspects of forgotten diseases affecting the world's people. Authors and readers will benefit from:

- Fast publication: a seamless electronic workflow which quickly puts articles online.
- Wide dissemination: open access making science globally available.
- Barrier-free communication for greater media coverage.
- Access in perpetuity: automatic deposit in PubMed Central ensures availability.
- No subscription fees: everyone can read and enjoy research.

Reference: PLoS at <http://www.plos.org>, <http://www.facebook.com>, and <http://www.plosone.org>