WHO Drug Information

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Announcement

The 15th International Conference of Drug Regulatory Authorities (ICDRA) will be hosted by the State Agency for Medicines, Estonia, in collaboration with the World Health Organization.

The ICDRA will take place in Tallinn, Estonia, 23 – 26 October 2012.

Information and registration at:
http://www.icdra.ee
http://www.who.int/medicines/icdra
WHO Prequalification of Medicines Programme

The Expert Review Panel

WHO prequalification of medicines for procurement by United Nations (UN) and other agencies has levelled the playing field by creating a competitive supply of quality products in response to donor demand. However, there are still too few WHO-prequalified or stringently authorized finished products available on the market to ensure a sustainable supply of medicines needed in treatment programmes. Since 2009, the WHO Prequalification of Medicines Programme (PQP) has been hosting and coordinating a novel quality risk assessment mechanism on behalf of the Global Fund to Fight AIDS, Tuberculosis and Malaria. The Expert Review Panel (ERP) assesses quality risks of pharmaceutical products which do not yet meet stringent quality requirements. Based on standardized, transparent criteria, it gives advice on whether each product is acceptable for procurement for the next 12 months.

In six review rounds, the ERP has assessed a total of 310 dossiers of antiretroviral medicines (ARVs), antituberculosis products and antimalarials, with a time frame of 4–6 weeks for completion of each round. The cost of ERP review is moderate as it is a once-off, abbreviated assessment. The outcomes have been crucial in securing a sustained supply of needed medicines, especially anti-TB products and some antimalarials.

The process has been well accepted by manufacturers and procurement agencies and has promoted progression of medicines to prequalification. Of 115 eligible products assessed by the ERP in 2009 and 2010, 44 became prequalified or approved by a stringent regulatory authority thereafter. Agencies have harmonized their quality assurance policies and are using the mechanism jointly with the Global Fund. This has resulted in unified quality standards and efficiency gains for all stakeholders.

The ERP approach could be adapted for assessment of additional product categories such as life-saving antibiotics or zinc for the treatment of diarrhoea in children. But it should be borne in mind that ERP is not intended to replace WHO prequalification or stringent regulatory assessment.

Incentives for manufacturers to submit products to ERP for evaluation may remain limited for medicines that have a market outside donor-funded programmes but this does not signify that such products need not adhere to stringent quality standards or that such standards should apply to donor-funded products only. On the contrary, WHO is working with manufacturers and regulators around the world to strengthen regulatory capacity in line with internationally accepted standards, so that all medicines are safe, effective and of good quality.
Quality policies in medicines procurement

Stringent standards for key medicines

Significant progress has been achieved in the last decade to increase access to medicines in low- and middle-income countries. The treatment of HIV, tuberculosis and malaria has attracted international funding. Competitively-priced medicines are now being sourced from emerging countries, especially India, and from local manufacture in some developing countries.

Presently, donors and healthcare workers are relying on the high standards of the PQP and stringent regulatory authorities (SRAs) (1, 2) to ensure the quality of products which they source from diverse regulatory environments (3). Likewise, the Medicines Patent Pool (4), which aims to bring down medicines prices through voluntary licensing of critical intellectual property from patent-holders, will require its licensees to submit their products to either the PQP or to an SRA for evaluation.

The Global Fund has played a leading role in promoting this development. From its inception in 2002, it has defined a formal quality policy for pharmaceutical products for implementation by its grant recipients, requiring WHO prequalification or SRA authorization for key products that are procured with its funds (2). As these funds account for a significant market share of key products, especially ARVs and artemisinin-based combination therapies (ACTs), the policy has had a significant market impact.

Alternative criteria to ensure continued supply

Despite an increasing demand by donors, WHO-prequalified or SRA-approved products are not available on the market for all needed medicines. To ensure a continued supply, alternative criteria must be applied to product selection that balance the benefit of treatment against quality risks of products which do not yet meet stringent standards. This can be a complex process, with decisions often made on a case-by-case basis.

Specialized agencies such as UNICEF and Médecins Sans Frontières (MSF) have developed their own systems to perform these risk reviews and the WHO Quality and Safety of Medicines (QSM) team in the Department of Essential Medicines and Health Products (EMP) supports the Global Drug Facility (GDF) (5) and UNITAID (6) in this respect. The outcomes of such reviews are shared among The Interagency Pharmacist Group comprising PQP, WHO procurement services, UNICEF, MSF, the International Committee of the Red Cross (ICRC), and the Global Fund. The Group works together by discussing the outcomes and challenges of risk reviews on a confidential basis.

The Global Fund has formally defined alternative quality criteria and has successively strengthened these over the years to encourage competition and promote prequalification. In 2008, it conducted a major policy review in wide consultation with stakeholders. The revised policy, effective since July 2009, applies stringent quality requirements to all ARVs, anti-TB products and antimalarials, and relies on a novel mechanism to ensure a continued supply of needed products not yet meeting these requirements: the Expert Review Panel. Based on some of the earlier risk assessment approaches developed by WHO and other agencies, this mechanism serves to assess product quality risks according to transparent criteria.

The Expert Review Panel

The ERP is an independent technical body hosted by WHO (7). It is composed of external regulatory experts and coordinated by QSM. To date, the ERP has met twice a year to review submissions
received in response to Global Fund invitations to manufacturers to submit an Expression of Interest (EOI), and to advise on whether or not each of the products concerned can be considered acceptable for procurement during the following 12 months. Ad-hoc reviews can be arranged for urgently needed products, for both the Global Fund and other interested parties.

Product data are submitted in questionnaire-type abridged dossiers based on a format published in WHO technical guidance (8) and further developed by the Interagency Pharmacist Group. The manufacturer can provide cross-references to more detailed information already submitted in a full prequalification dossier.

The ERP coordinator manages the selection of ERP members, ensures that they remain current with latest PQP and SRA guidelines, arranges timely review of submissions and advises the Global Fund on the acceptability for procurement of each specific finished product, based on the results of the ERP review.

**Eligibility criteria for ERP review**

To be eligible for ERP review, a product must be manufactured at a site and on a production line complying with good manufacturing practices (GMP) as determined by PQP, an SRA or a member of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S) (9). Before ERP finalizes its advice, it will verify the GMP status of each product with the PQP inspectorate.

Secondly, a product dossier must already have been accepted for review, after screening for completeness, by PQP or a stringent regulatory authority. Most submissions received since 2009 had been in the pipeline for prequalification, although approximately 40% of HIV-related products submitted to ERP had been submitted to the US Food and Drug Administration (FDA) for evaluation and tentative approval under the President’s Emergency Plan for AIDS Relief (PEP-FAR) (10) but not to PQP.

Some needed products are not on the EOI list for WHO prequalification. These products have no pathway for prequalification, and are also unlikely to be submitted for marketing approval in a country with an SRA. Medicines in this group include special strengths of anti-TB medicines used in India, and older, non-artemisinin-based antimalarials still used in certain regions and situations. The ERP will review such products even if they are not under assessment by a stringent body, as long as they are manufactured in compliance with international GMP standards.

**Transparent assessment criteria**

The ERP assesses four main quality elements, and categorizes each product into one of four risk categories (see Table 1).

As most innovator products have been assessed and registered in countries with stringent regulatory environments, the ERP’s review mechanisms are geared towards rapid review of generic products rather than the safety and efficacy aspects of new molecules. The exception has been DHA-piperaquine, an artemisinin-based combination antimalarial developed and registered in China: not considered an SRA as defined by the Global Fund (1). Submissions from two manufacturers were reviewed by the ERP and assigned to risk category 4 because the data provided was not sufficient to assign them to category 1, 2 or 3.

**Time-limited advice**

The ERP’s advice is valid for 12 months. During this time, the product is expected to progress to WHO prequalification or SRA-approval. For products in risk categories 1 and 2, manufacturers can apply for an extension by submitting an updated dossier and a progress report on the product’s progression towards stringent approval.
Products in risk categories 1 and 2 are included on the Global Fund on-line product list (11), together with the date until which the ERP’s advice will remain valid. Grant recipients can conclude procurement contracts until the last day of the validity period, for a maximum duration of one year.

**Use of the ERP mechanism by agencies**

**Harmonization**

The Global Fund invites EOIs for ERP review twice a year for medicines which are on the WHO EOI list for prequalification, and for which there are fewer than three WHO-prequalified or SRA-authorized finished products on the market. The ERP mechanism builds on experience with WHO’s ad hoc quality risk reviews performed before 2009 for GDF and UNITAID, providing an opportunity for these organizations to harmonize their quality standards.

During 2009, the Global Fund and GDF organized separate quality risk reviews and, after a thorough review of the processes used, mutually recognized the outcome of the ad hoc reviews that each agency had organized. From 2010 onwards, GDF and UNITAID have provided input to the EOIs issued by the Global Fund for ERP review of medicines for TB and HIV/AIDS, respectively. UNICEF has been reviewing dossiers as part of its ACT tender process with WHO, and will adapt this process to link it with the ERP procedure as of 2012.

**Process and timelines**

On receipt of submissions, the Global Fund liaises with manufacturers, screens dossiers for completeness and forwards...
the submissions to the ERP Coordinator ahead of each session. In the first six ERP sessions, 79% of submissions received were eligible and complete and were forwarded for review.

In its first six sessions, the ERP assessed between 15 and 96 submissions per session. The median turn-around time from the start of the review until communication of final advice by the ERP Coordinator to the Global Fund was 35 calendar days (17–49 days). The session-based system has proved efficient, with predictable timelines for manufacturers and agencies.

Outcomes of reviews
In the first six sessions, the ERP assessed 310 submissions (involving 220 products), and had no objections to procurement of 74 products.

Only products under assessment by PQP or an SRA can be classified in risk categories 1 or 2 (“no objection”), and this was the case with two-thirds of ARVs, about a third of anti-TB products and less than one in eight of the antimalarials assessed.

Among the products not under stringent assessment, more than half of the anti-TB products and a third of the antimalarials were considered acceptable for procurement in exceptional situations.

Major deficiencies identified
The ERP identified major deficiencies in 253 of the 310 submissions. Figure 1 shows the percentage of dossiers in each product category which had major deficiencies. For some products, additional information was subsequently submitted.

Figure 1. Frequency of major deficiencies in ERP submissions (Rounds I to VI)

<table>
<thead>
<tr>
<th>Specification</th>
<th>Stability data</th>
<th>Efficacy data (bioequivalence)</th>
<th>Active Pharmaceutical Ingredients (API)</th>
</tr>
</thead>
</table>
by the manufacturer, so that ultimately they formed part of the group of 74 products, each of which was categorized in category 1 or 2.

As Figure 1 shows, problems for ARVs related mostly to specifications and incomplete stability data. Anti-TB products were the only products to have GMP issues with respect to active pharmaceutical ingredients (APIs). Antimalarials had unsatisfactory specifications, and problems with stability and efficacy data were observed more frequently than in other medicines. As can be expected, insufficient or missing data were most common among products that were not under stringent assessment.

Progression towards stringent approval
Of the 115 products reviewed by the ERP between June 2009 and November 2010, 44 (38%) had become WHO prequalified or SRA-authorized as at March 2012 (see Figure 2). For products reviewed in 2011, it is too early to estimate the rate of progression; but already by March 2012, two ARVs, one anti-TB product and two variations of anti-TB products have become prequalified, and others may follow.

Thirty-four of 56 favourably reviewed products — compared with 10 of 59 unfavourably reviewed ones — progressed to stringent approval, meaning that categorization of a product in category 1 or 2 (which may be considered as a positive categorization) has a good predictive value. Most of the successful products progressed to WHO prequalification; some ARVs progressed to FDA tentative approval under PEPFAR, and many of these also became WHO prequalified.

The ten unfavourably reviewed products that progressed to stringent approval were all reviewed in the first two ERP sessions. Manufacturers thereafter submitted improved dossiers directly to a stringent assessment body without re-submitting them to ERP.

Extension of ERP advice
Four months before the expiry of ERP advice, the Global Fund contacts manufacturers of products classified into categories 1 or 2 to provide a progress report and additional product data. Based on this information, the ERP will consider extending its advice for another year. Of the 28 products relating to ERP sessions I to VI, the ERP granted an extension in

Figure 2. Progression of eligible ERP-reviewed products (2009–2010) to prequalification or SRA approval

<table>
<thead>
<tr>
<th>Subsequently approved by PQP or an SRA (as at March 2012):</th>
<th>yes</th>
<th>no</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERP objection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARVs</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Anti-TB products</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>25</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No ERP objection</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ARVs</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Anti-TB products</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
five cases and a further five products became WHO-prequalified while extension was being considered. The remaining 18 were not granted an extension. Extension of ERP advice has thus been the exception rather than the norm.

**Procurement decisions**
Although the ERP advises on procurement of a product, donors and procurement entities are responsible for deciding on the use of the product in the treatment programmes that they support. Although the Global Fund lists products classified in categories 1 and 2 on its web site for information of grant recipients and other organizations, grant recipients must obtain the Global Fund’s approval before procurement of an ERP-reviewed product.

Products in risk category 3 are not listed, and will be funded only if experts of the respective WHO disease programme have confirmed that the treatment benefit in each specific context outweighs the quality risk identified by the ERP. If not, grant recipients can either work with the Global Fund to identify an acceptable clinical alternative, or they can purchase the product at their own risk and expense.

As an additional safeguard, batches of all ERP-reviewed products must pass random quality control testing before shipment.

**Past procurement of ERP-reviewed products**

**Use by Global Fund grant recipients**
Most ARVs and antimalarials, and a significant proportion of anti-TB medicines reviewed by the ERP are procured with Global Fund grants. According to the Global Fund’s online Price and Quality Reporting (PQR) database as at 31 October 2011, recipients had reported purchasing ERP-reviewed products worth US$ 13.2 million since July 2009. In value terms, this corresponded to 13% of all first-line anti-TB products (including streptomycin), 5% of all antimalarials and 0.6% of all ARVs reported as procured. Second-line anti-TB products were approved by the Green Light Committee until the second half of 2011 and were therefore not yet reported as ERP-reviewed products.

The use of ERP-reviewed products has increased. During 2011, the Global Fund received 88 funding requests for ERP-reviewed anti-TB products and 32 for antimalarials (compared with 48 and 7 respectively in 2010). Two requests for ARVs were received in 2012 — the first since June 2009.

These figures reflect the availability of prequalified, SRA-authorized and ERP-reviewed products in each of the three disease categories.

- For ARVs, a wide choice of prequalified or SRA-authorized products is available. Few ERP-reviewed products are needed, mainly for new paediatric formulations, and where stringently assessed products are not accessible due to patent issues.

- For anti-TB medicines, WHO prequalified finished products are available but ERP-reviewed products have been crucial in securing a continued, competitive supply. Requests are increasing for ERP-reviewed products for second-line treatment.

- For antimalarials, the numbers of WHO prequalified and of ERP-reviewed product choices are the lowest. The Global Fund list of January 2012 proposes 19 prequalified or SRA-authorized formulations, for 17 of which there was only one supplier. No ERP-reviewed product was listed for general use, although some non-artemisinin-based products can be procured under exceptional circumstances.

**Quality control testing outcomes**
In 2010 and 2011, the Global Fund and
GDF jointly arranged for pre-shipment quality control testing of almost 800 batches of ERP-reviewed products by competitively selected WHO-prequalified laboratories. All batches passed the testing, although in a few cases non-compliant results were initially reported due to methodological and interpretation issues. Certificates of analysis for all batches tested are available on the Global Fund web site (12). This experience suggests firstly that quality problems at the pre-shipment stage in the supply chain are rare. It also underscores the importance of in-country quality monitoring. Many quality problems will only emerge once the product has been received, stored and distributed in the destination country. It also demonstrates that coordination and communication between manufacturers, procurement agencies, laboratories and recipients — for organizing efficient testing and correct interpretation of test results — are crucial.

**Proven public health impact of the ERP**

**Securing the supply of needed products**

The ERP mechanism has proved effective to support procurement of needed medicines of which there are not enough WHO-prequalified or SRA-authorized finished products available, avoiding treatment disruption and mitigating the risk of stock outs.

The impact has been greatest for anti-TB medicines. A core group of manufacturers have been submitting dossiers to ERP and working towards prequalification of their products, and two sources of finished products are now available for most medicines. This has helped to achieve shorter lead times and competitive prices.

Moreover, a successful transition was made whereby GDF procurement policy was harmonized with that of the Global Fund (13). Some initial price increases did occur before a competitive supply of quality-assured products was established. But this was only in a few cases. ERP review has also helped to secure a sustainable supply of some second-line products for which the production capacity of individual suppliers is limited.

**A single process with unified requirements**

Major procurement actors are harmonizing their quality assurance policies (14–15) to incorporate the ERP process, which is both defined and flexible enough to result in useful procurement outcomes. This has resulted in efficiency gains not only for procurement agencies but also for manufacturers, since they can now follow a single quality assurance process with transparent, unified requirements.

**Interim risk assessment leads to stringent approval**

The ERP review mechanism has challenged initial concerns that it might duplicate prequalification and merely add another layer of procedures. To the contrary, ERP review complements WHO prequalification, as shown by the rates of progression in Figure 2.

The mechanism works best where it is linked to WHO prequalification, which — unlike marketing authorization in a country with an SRA — will ensure regular follow up and requalification in the destination countries.

Manufacturers have welcomed this process, which has helped them to bring needed products to market quickly while progressing towards WHO prequalification. The intensive communication during each ERP session has in some cases laid the groundwork for speedy development of full dossiers for submission to the PQP. Twelve of 19 anti-TB products and all three antimalarials which have been prequalified since 2009 had been submitted to the ERP.
Challenges

Incentives for ERP review
Incentives for manufacturers to meet the stringent quality requirements of donors are currently limited when other than donor-funded markets are available. Moreover, donor-funded markets are often fragmented, with inaccurate forecasting and frequent payment issues. To invest in quality systems, manufacturers require a prospect of predictable sales over a period of several years, possibly across product categories. Advance information on the magnitude of the quality investment they are required to make in order to meet international quality standards and potential sales would be helpful. However, these are influenced by many factors and are difficult to project.

Ongoing availability of quality-assured products
Unexpected quality issues can arise in connection with any of the quality elements of a product that has been assessed by the ERP. These can result in de-listing or downgrading of an ERP-reviewed product. For example, a notice of concern issued by PQP for an API recently affected the quality status of several anti-TB products from different suppliers. In 2011, PQP started to prequalify APIs, hopefully reducing the likelihood of this particular issue arising in the future. More generally, the example emphasizes the importance of diversified supply sources and of vigilance in procurement by verifying that the product purchased has the same specifications as the WHO prequalified or ERP-reviewed product.

Future perspectives

ERP reviews of additional essential medicines
The ERP mechanism has been well accepted by manufacturers and procurement agencies, and clearly continues to be needed to support procurement of anti-malarials, anti-TB products and reproductive health products in compliance with quality assurance policies.

Donors, procurement agencies and implementers are also considering whether to introduce more stringent requirements — including stringent follow-up in recipient countries — for other essential medicines. Obvious candidates include products on the PQP EOI lists, such as life-saving antibiotics and zinc for treatment of diarrhoea in children.

Not all essential medicines needed by agencies are currently on PQP’s EOI lists. If the ERP mechanism were to be used to ensure the quality of these medicines, methods would need to be designed to ensure regular follow-up. Currently, the ERP provides interim advice only. It is not designed to verify continued compliance of manufacturers with stringent quality standards on an ongoing basis.

For certain product groups, such as life-saving antibiotics that are vulnerable to emerging resistance, modification of ERP eligibility and assessment criteria might be justified, provided sufficient technical rationale can be demonstrated. However, more work would be needed to group such products in risk-based categories and to determine the technical criteria that the ERP should apply to each product group to mitigate any risks.

Cost recovery
Although ERP review has proved to be rapid and cost-effective, the cost will increase if dossiers for additional products are reviewed. The cost of administrative and communication support which has so far been assured by the Global Fund must also be considered. In the future, a full cost recovery system may be envisaged to make ERP review a sustainable mechanism for wider use.

Replication of the ERP mechanism may seem an attractive prospect from the point of view of ensuring a continued supply of needed products across differ-
ent therapeutic categories. However, this could lead to divergent standards and procedures — potentially weakening the unified approach that has been the ERP’s major strength.

**Beyond donor-funded programmes**

Medicines quality has very real implications for patients and for public health. The ERP mechanism is a unique tool for supporting evidence-based decision-making in procurement of needed treatment options. It has also raised awareness of medicines quality issues among suppliers and recipients.

However, stringent quality assurance cannot and should not remain limited to donor-funded medicines. WHO is working with regulatory authorities around the world to implement internationally accepted quality standards across the board.


**References and notes**

1. Up to 30 June, the Global Fund’s Quality Assurance Policy for Pharmaceutical Products defined an SRA as a member of ICH or (PIC/S) and, as of 1 July 2009, as a member, observer or associate of ICH through a legally binding mutual recognition agreement. ICH is the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and PIC/S is the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (jointly referred to as PIC/S).


6. UNITAID, at http://www.unitaid.eu


Safety and Efficacy Issues

Tolvaptan: risk of serious neurological events

United Kingdom — Treatment with tolvaptan (Samsca®) can result in over-rapid correction of hyponatraemia leading to serious neurological events. Careful monitoring of serum sodium is therefore important and co-administration of other drugs that may increase serum sodium is not recommended. Tolvaptan may also reduce the effect of vasopressin analogues used to control or prevent bleeding.

Tolvaptan is a selective vasopressin V2-receptor antagonist licensed in the UK since 2009 for the treatment of adults with hyponatraemia secondary to inappropriate antidiuretic hormone secretion (SIADH) at a dose of 15–60 mg once a day.

Serum sodium should be closely monitored in patients receiving tolvaptan, especially those with very low serum sodium at baseline or where there is increased risk of demyelination syndromes. Increases in serum sodium which are too rapid can be harmful and cause osmotic demyelination, resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma, or death.


Strontium ranelate: new contraindications and revised warnings

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has finalized a review of strontium ranelate (Protelos® and Osseo®), indicated for treatment of osteoporosis in postmenopausal women. The Committee concluded that these medicines remain an important treatment but that changes to the prescribing advice are necessary to better manage associated risks.

The review was initiated following publication of a study in France identifying 199 severe adverse reactions reported with these medicines from January 2006 to March 2009. Around half of these were VTE events, and about a quarter related to skin reactions. The CHMP has reviewed all available data which show that the risk is higher in patients with a history of VTE, as well as in patients who are temporarily or permanently immobilized.

Data also show that the incidence rate of serious skin reactions is low and no possible mechanism of action has been identified so far.


Fingolimod: new safety advice

European Union — The European Medicines Agency (EMA) recommends new advice to healthcare professionals to reduce the risk of adverse effects on the heart associated with the use of the multiple sclerosis (MS) treatment fingolimod (Gilenya®).

Following a review, the Agency’s Committee for Medicinal Products for Human Use (CHMP) recommends that doctors should not prescribe fingolimod to patients with a history of cardiovascular and cerebrovascular disease or who take
heart-rate lowering medication. However, when treatment with fingolimod is considered necessary, heart activity should be monitored at least overnight following the first dose of fingolimod and doctors should seek advice from a cardiologist on appropriate monitoring.

Fingolimod has been authorized in the EU since March 2011 for the treatment of relapsing-remitting MS in patients who have not responded to treatment with beta-interferon or whose disease is severe and getting worse rapidly. It is the first disease-modifying MS treatment available as an oral formulation.


Pioglitazone: bladder cancer

Canada — Important safety information has been released concerning a potential risk of bladder cancer in patients treated with pioglitazone hydrochloride (Actos®).

Pioglitazone, an oral anti-diabetic drug, is authorized in Canada in patients with type 2 diabetes mellitus as an adjunct to decrease blood glucose levels not controlled by diet and exercise alone. It is also indicated in combination with a sulfonylurea or metformin when diet and exercise plus the single agent do not result in adequate glycaemic control.

- Findings from new studies reveal that there is a potential increased risk of bladder cancer in patients treated with pioglitazone-containing products.
- Pioglitazone is now contraindicated in patients with active bladder cancer, a history of bladder cancer or uninvestigated macroscopic haematuria. Any macroscopic haematuria should be investigated before starting pioglitazone therapy.

- Risk factors for bladder cancer should be assessed before initiating treatment with pioglitazone.
- Patients prescribed pioglitazone should be advised to seek medical attention if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment, as these may be symptoms of bladder cancer.


Benzocaine: new risk statements

Canada — Health Canada has requested companies to add new risk statements to the packaging and labelling of licensed benzocaine products. Health Canada has advised of certain health risks associated with benzocaine products, including methemoglobinemia. The label changes apply to all benzocaine products except lozenges.

The new risk statements provide added instructions with respect to the risk of methemoglobinemia and for safe product use, including the importance of using the smallest amount possible.


Minocycline: lupus erythematosus and autoimmune hepatitis

Canada — Minocycline is a second-generation tetracycline that exhibits both antibacterial and anti-inflammatory properties.

Because the pathogenesis of acne can include bacterial proliferation (*Propionibacterium acnes*) and inflammation, oral antibiotics such as tetracyclines are frequently prescribed for the treatment of moderate to severe acne. Response
to oral antibiotics is usually seen after at least six weeks of therapy, and treatment can last for several months.

The occurrence of autoimmune disorders, such as lupus erythematosus and autoimmune hepatitis, has been associated with the use of a number of products, including minocycline. Drug-induced lupus erythematosus can produce symptoms that include myalgia, arthralgia and serositis, as well as abnormal laboratory results such as elevated markers of inflammation and the presence of antinuclear antibodies.

Minocycline-induced autoimmune hepatitis shares many characteristics with autoimmune hepatitis, such as the presence of antinuclear and antismooth-muscle antibodies, elevated immunoglobulin levels and histologic features.

As of 30 September 2011, Health Canada has received four reports of drug-induced lupus erythematosus and three reports of autoimmune hepatitis suspected of being associated with minocycline use in adolescents. All the adverse reactions (ARs) were serious, involved the use of minocycline for the treatment of acne and occurred between 2004 and 2009.

If minocycline-induced autoimmune hepatitis is unrecognized and drug exposure continues, hepatic fibrosis and chronic liver disease may develop.

Extracted from Canadian Adverse Reaction Newsletter, Volume 22, Issue 2, April 2012 at http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v22n2-eng.php#article1

References


Domperidone maleate: ventricular arrhythmias and cardiac death

Canada — Healthcare professionals have been informed that the gastrointestinal motility modifier, domperidone, should be initiated at the lowest possible dose in adults. Recent epidemiological studies have shown that the use of domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death, particularly in patients taking daily doses greater than 30 mg, and in patients older than 60 years of age.

Domperidone is indicated in adults for the symptomatic management of upper gastrointestinal motility disorders associated with chronic and subacute gastritis and diabetic gastroparesis. Domperidone is also indicated to prevent gastrointestinal symptoms associated with the use of dopamine agonist antiparkinson agents.

Caution should be exercised when using domperidone concomitantly with drugs that prolong the QT interval, in patients who have existing prolongation of cardiac conduction intervals, particularly QTC, and in patients with significant electrolyte disturbances or underlying cardiac disease such as congestive heart failure.


Vandetanib: risk of fatal outcome

Canada — Health Canada has issued safety information regarding vandetanib (Caprelsa®) approved as monotherapy for the treatment of symptomatic or progressive medullary thyroid cancer in adult patients with unresectable locally advanced or metastatic disease.

- Vandetanib can prolong the QTc interval and cases of Torsade de Pointes and sudden death have been reported in clinical trials.
- Vandetanib is only available through a Restricted Distribution Programme where physicians are required to complete mandatory online training.

In addition to QTc interval prolongation, Torsade de Pointes, sudden death, rash and other skin reactions, diarrhoea, hypertension and vision abnormalities have also been reported.


Finasteride and dutasteride: prostate cancer

Canada — Health Canada has informed healthcare professionals that finasteride and dutasteride may be associated with an increased risk of developing rare, high-grade prostate cancer.

Finasteride is available under the brand names Proscar® and Propecia® and their generic equivalents. Dutasteride is available under the brand names Avodart® and Jalyn®. Finasteride and dutasteride are for use in men only. Proscar®, Avodart®, and Jalyn® are used for the treatment of benign prostatic hyperplasia (BPH), which is an enlargement of the prostate that is not cancerous. BPH is a common condition in men over 40. Propecia® is used to treat male pattern hair loss.

The new safety information is based on a review of two large international clinical trials: the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. The trials showed that long-term daily use of finasteride and dutasteride in men aged 50 years and older was associated with a small but statistically significant increased risk of high-grade prostate cancer. Propecia® was not included in these trials but a potential risk has not been ruled out.


Lenalidomide: increased malignancies

Canada — Health Canada has issued information regarding lenalidomide (Revlimgid®) capsules. Lenalidomide is an antineoplastic and immunomodulatory agent indicated for the treatment of transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS). Lenalidomide is also indicated in combination with dexamethasone for the treatment of multiple myeloma (MM) in patients who have received at least one prior therapy.

- An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated multiple myeloma patients receiving lenalidomide and dexamethasone compared to controls.
- In clinical trials of newly diagnosed multiple myeloma (not an authorized indication in Canada), a 4-fold increased incidence of SPM has been observed in patients receiving lenalidomide.
The risk of occurrence of SPM must be taken into account before initiating treatment with lenalidomide. Physicians should carefully evaluate patients before and during treatment to screen for the occurrence of new malignancies.


Antithrombotic medicines and bleeding

New Zealand — Antithrombotics are widely used to treat a number of conditions and guidance on their use has recently been issued by the Best Practice Advocacy Centre (BPAC). Bleeding is the major risk associated with all antithrombotics. The Centre for Adverse Reaction Monitoring (CARM) continues to receive reports of serious bleeding experienced by patients taking these medicines.

An overview of 12 months of reports to CARM showed that the main sites of serious bleeding were most often gastrointestinal or intracranial in origin. Although combination therapy is recommended for some conditions, adverse reaction data continues to indicate a major risk factor for bleeding to be the concomitant use of more than one antithrombotic medicine.


Belimumab: hypersensitivity and infusion reactions

Canada — Health Canada has issued information regarding hypersensitivity and infusion reactions associated with belimumab (Benlysta®) indicated, in addition to standard therapy, for adult patients with active, auto-antibody-positive, systemic lupus erythematosus.

Recently, a number of post-marketing reports concerning serious acute hypersensitivity reactions have been received globally. Health professionals have been informed that:

• Administration of belimumab may result in infusion and hypersensitivity reactions.
• Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk.
• In clinical trials, severe and/or serious infusion or hypersensitivity reactions were reported in 1.2% and 0.6% of subjects receiving belimumab 10 mg/kg and placebo, respectively.


Escitalopram: abnormal heart rhythm

Canada — Clinical trial data has shown that escitalopram (Cipralex®), a selective serotonin reuptake inhibitor (SSRI), can cause life threatening QT interval prolongation. A warning and dosing recommendations have been added to the drug label.

• Escitalopram should not be used in patients with congenital long QT syndrome, or in patients with QT interval prolongation.
• Use of escitalopram is discouraged in patients who are also taking drugs that prolong QT interval or that decrease electrolyte levels in the body.
• 10 mg per day is the maximum recommended dose for patients who are 65 years of age or older, have liver problems or are taking the heartburn drugs omeprazole or cimetidine.

Empowering patient ADR reporting

The Monitoring Medicines (MM) Project was developed within a wider WHO strategy Optimizing drug safety monitoring to enhance patient safety and achieve better health outcomes. It began in September 2009 and is coordinated by the Uppsala Monitoring Centre (UMC), Sweden, with funds from the European Commission.

The MM Project aims to improve patient safety both within the European Union and in other regions. One objective is to support and strengthen consumer reporting of suspected adverse drug reactions (ADRs). The project consortium comprises eleven partners representing a wide range of organizations dedicated to improving public health through the safe use of medicines.

An increasing number of consumers are being encouraged to report adverse reactions to medicines. Organizations such as WHO and the European Commission acknowledge the role of the consumer in spontaneous reporting.

In 2008, representatives of national pharmacovigilance centres requested WHO to develop a handbook on how to establish a reporting system for medicine-related problems for the general public. Implementation of this task became feasible within the objectives of the MM Project. A WHO guidance document Safety Monitoring of Medicinal Products – Reporting system for the general public is now available as a direct project deliverable.

In tandem with this development, the UMC has been working on a tool to support consumer reporting of ADRs. Several patient organizations have provided their inputs in developing this tool. The WHO guidance document and tool were introduced to pharmacovigilance centres and consumer/patient organizations at a recent workshop in the Netherlands, 7–9 March 2012.

Piloting the UMC patient reporting tool in selected countries and any subsequent adaptation of the tool will form the next steps in this journey towards patient empowerment in pharmacovigilance.


Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious or 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

Commercially confidential information and personal data

European Union — The Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMA) have adopted a joint guidance document providing a consistent Europe-wide approach to the identification of commercially confidential information (CCI) and personal data (PPD) in a marketing authorization application.

In future, regulatory authorities in the European Economic Area (EEA) will apply the same principles to identify which parts of an application dossier can or cannot be released in response to requests to access documents. This is regardless of whether the medicine concerned has been authorized using the centralized, mutual recognition or decentralized procedures.

The guidance document limits the scope of what information regulators will consider to be commercially confidential in a marketing authorization application. The exceptions mainly relate to information about quality and manufacturing of a medicine, as well as information about facilities or equipment and some contractual arrangements between companies.

In addition, the guidance document sets out how personal data as defined by the EU Directive 95/46/EC will be protected if it can lead to the identification of a person. The document gives further guidance on how to identify personal data relating to experts, staff or patients that should be redacted.

Dossiers such as orphan designations, paediatric investigation plans and veterinary medicines are not covered by the guidance. Together with those applications that have been withdrawn or rejected, these will be handled by regulators according to their existing practices and legal provisions.

The two guidance documents should be interpreted jointly.

- HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the Marketing Authorization (MA) Application – release of information after the granting of a Marketing Authorization
- Principles to be applied for the implementation of the HMA/EMA Guidance on the identification of CCI and PPD in MA Applications


Pyronaridine and artesunate: new anti-malarial approved

European Union — The European Medicines Agency (EMA) has recommended Pyramax®, a fixed combination consisting of pyronaridine and artesunate for the treatment of acute, uncomplicated malaria infection caused by Plasmodium falciparum or by Plasmodium vivax in adults and children weighing 20 kg or more in areas of low transmission with evidence of artemisinin resistance.

The scientific opinion for Pyramax® was given under Article 58 of Regulation (EC) No 726/2004, which allows the Agency’s Committee for Medicinal Products for Human Use (CHMP) to give a scientific opinion, in cooperation with the World
Health Organization (WHO), on medicines for human use intended exclusively for markets outside the European Union (EU). Applicants can use the CHMP’s scientific opinion as a basis when applying for a marketing authorization in countries outside of the EU. The scientific opinion also facilitates the WHO prequalification process.

Due to concerns about severe liver problems associated with repeated use, Pyramax® should only be used as a single 3-day treatment course in areas of low transmission with evidence of decreased efficacy of other oral artemisinin-based combination therapies, consistent with WHO recommendations. Pyramax® should only be used at controlled sites where a patient’s liver function can be systematically monitored and where exhaustive collection of adverse events as well as reliable information on resistance can be ensured.


Aprotinin: suspension lifted

European Union — The European Medicines Agency (EMA) has recommended that suspension of the marketing authorizations for aprotinin-containing medicines in the European Union (EU) be lifted. This follows a full review of the benefits and risks of all antifibrinolytic medicines, which found that the results of the BART study on which the suspension was based are unreliable. Prior to its suspension in 2008, aprotinin was authorized for patients undergoing heart bypass surgery.

The Agency’s Committee for Medicinal Products for Human Use (CHMP) has now concluded that aprotinin’s benefits in preventing blood loss outweigh its risks in patients undergoing isolated heart bypass surgery who are at high risk of major blood loss.

The Committee found that the BART study’s results were not replicated in other studies and that the overall data available showed that aprotinin’s benefits are greater than its risks in the restricted indication.


Pixantrone: conditional approval for non-Hodgkin B-cell lymphoma

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has recommended that pixantrone (Pixuvri®) be granted conditional approval for non-Hodgkin B-cell lymphoma. The new medicine is to be used alone in patients whose cancer is aggressive and has come back after multiple rounds of previous chemotherapy or is not responding to other treatments.

The Committee recommended conditional approval because the data supplied show that the medicine’s benefits outweigh its risks but are not yet comprehensive. The most frequent side-effect seen in clinical studies was suppression of bone marrow, resulting in low levels of white blood cells, platelets and red blood cells. Infections were common but were only serious in a few patients.


Levofloxacin approved for plague

United States of America — The Food and Drug Administration (FDA) has approved levofloxacin (Levaquin®) to treat patients with plague. The agency also approved the drug to reduce the risk of plague after exposure to Yersinia pestis. The three most common forms of plague are bubonic, pneumonic and septicemic plague.
Common side effects reported in more than 3% of patients were nausea, headache, diarrhea, insomnia, constipation, and dizziness. Serious but rare side effects include tenosynovitis and tendon rupture, worsening of muscle weakness in people with the neuromuscular disorder myasthenia gravis, allergic reactions, liver damage, abnormalities of the blood, effects on the nervous system, and abnormal heart rhythm.


Pazopanib: approved for soft tissue sarcoma

United States of America — The Food and Drug Administration (FDA) has approved pazopanib (Votrient®) to treat patients with advanced soft tissue sarcoma who have previously received chemotherapy. The drug is not approved for patients with adipocytic soft tissue sarcoma and gastrointestinal stromal tumours.

The most common side effects reported were fatigue, diarrhoea, nausea, weight loss, high blood pressure, decreased appetite, vomiting, tumour and muscle pain, hair color changes, headache, a distorted sense of taste, shortness of breath, and skin discoloration.

Pazopanib carries a boxed warning alerting patients and health care professionals to the potential risk of hepatotoxicity, which can be fatal. Patients should be monitored for liver function and treatment should be discontinued if liver function declines.

Votrient® was first approved in October 2009 for the treatment of advanced kidney cancer.


Florbetapir: approved to estimate brain amyloid plaque content

United States of America — The Food and Drug Administration (FDA) has approved Florbetapir F 18 Injection (Amyvid®) a drug for positron emission tomography (PET) imaging of the brain in adults who are being evaluated for Alzheimer disease and other causes of cognitive decline. Amyvid® is used to produce PET scans that estimate the brain β-amyloid neuritic plaque density in patients with cognitive impairment. Until now, this could only be determined with a brain biopsy or examination of the brain at autopsy. Following intravenous injection, Amyvid® binds to brain β-amyloid. A radioactive signal is detected and produces images of the plaque in the brain.

Common adverse reactions include headache, musculoskeletal pain, fatigue, and nausea.


Capsaicin: withdrawal of marketing authorization application

European Union — The European Medicines Agency (EMA) has been notified of the manufacturer's decision to withdraw the application for an extension of the therapeutic indication for the centrally authorized medicine capsaicin (Qutenza®), 179 mg cutaneous patch.

Capsaicin was first authorized in the European Union on 5 May 2009 and it is currently indicated for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain.

The application was withdrawn based on the CHMP’s view that the data provided do not allow the Committee to conclude on a positive benefit-risk balance for the extension.

**Rivastigmine: withdrawal of marketing authorization application**

-European Union—The European Medicines Agency (EMA) has been notified of the manufacturer's decision to withdraw the application for an extension of the therapeutic indication for the centrally authorized medicine rivastigmine (Exelon® and Prometax®) 4.6 mg/24 h and 9.5 mg/24 h transdermal patches. The transdermal patches are currently indicated for the symptomatic treatment of mild to moderately severe Alzheimer dementia. The application requested an extension of indication to include the symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson disease. The application was withdrawn because the additional data required could not be generated within the timeframe allowed in the centralized procedure.


**Megestrol: withdrawal of marketing authorization application**

-European Union—The European Medicines Agency (EMA) has been notified of the manufacturer’s decision to withdraw the application for a centralized marketing authorization for megestrol (Megestrol Alkermes®), 125 mg/ml oral suspension. Megestrol was intended to be used for the treatment of anorexia, cachexia or an unexplained significant weight loss in adult AIDS and oncology patients. The application was withdrawn following company portfolio prioritization.


**Lapatinib: withdrawal of marketing authorization application**

-European Union—The European Medicines Agency (EMA) has been notified of the manufacturer’s decision to withdraw the application for a centralized marketing authorization for an extension of the therapeutic indication for the centrally authorized medicine lapatinib (Tyverb®), 250 mg film-coated tablets.

Tyverb® was intended to be used in combination with paclitaxel for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2 (ErbB2). The patients in the registration study were not previously treated with trastuzumab in either the adjuvant or metastatic setting. At the time of withdrawal, the application was under review by the Agency’s Committee for Medicinal Products for Human Use (CHMP).

Lapatinib is currently authorized:

- For treatment of patients with breast cancer whose tumors overexpress HER2 (ErbB2).
- In combination with capecitabine for advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.
- In combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy.


ATC/DDD Classification

ATC/DDD Classification (Temporary)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology in March 2012. Comments or objections to the decisions should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology at whocc@fhi.no. The new ATC codes and DDDs will be considered final and be included in the January 2013 issue of the ATC Index. The inclusion of a substance in the lists does not imply any recommendation for use in medicine or pharmacy.

New ATC 5th level codes:

<table>
<thead>
<tr>
<th>ATC level</th>
<th>INN Common name</th>
<th>ATC code</th>
</tr>
</thead>
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<tr>
<td></td>
<td>metformin and alogliptin</td>
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<td>trenonacog alfa</td>
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<td>peginesatide</td>
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<td>tamsulosin and solifenacin</td>
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New ATC level codes (other than 5th level):

Direct factor Xa inhibitors B01AF
Fluoroquinolones S01AE

ATC code changes:

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<th>INN Common name</th>
<th>Previous ATC</th>
<th>New ATC</th>
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<tr>
<td>prucalopride</td>
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### ATC name changes:

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<tr>
<td>Drugs for functional bowel disorders</td>
<td>Drugs for functional gastrointestinal disorders</td>
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<td>Other drugs for functional bowel disorders</td>
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<td>Drugs for constipation</td>
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<td>Drugs for constipation</td>
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New DDDs:

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Herbal medicinal products*

* Assessed and approved by regulatory authorities based on dossiers including efficacy, safety, and quality data (e.g. the well-established use procedure in EU).

New ATC 5th level codes:

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<tr>
<td>Hederae helcis folium</td>
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* Assessed and approved by regulatory authorities based on dossiers including efficacy, safety, and quality data (e.g. the well-established use procedure in EU).
ATC/DDD Classification

ATC/DDD Classification (Final)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology in October 2011. They will be included in the January 2013 version of the ATC Index. The inclusion of a substance in the lists does not imply any recommendation for use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted at whoccs@fhi.no.

New ATC 5th level codes:

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<td>emtricitabine, tenofovir disoproxil, elvitegravir and cobicistat</td>
<td>J05AR09</td>
</tr>
<tr>
<td>faropenem</td>
<td>J01DI03</td>
</tr>
<tr>
<td>fidaxomicin</td>
<td>A07AA12</td>
</tr>
<tr>
<td>florbetapir ((^{18})F)</td>
<td>V09AX05</td>
</tr>
<tr>
<td>fluoxetine and psycholeptics</td>
<td>N06CA03</td>
</tr>
<tr>
<td>flutemetamol ((^{18})F)</td>
<td>V09AX04</td>
</tr>
<tr>
<td>glycopyrronium bromide</td>
<td>R03BB06</td>
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<tr>
<td>ingenol mebutate</td>
<td>D06BX02</td>
</tr>
<tr>
<td>ivacaftor</td>
<td>R07AX02</td>
</tr>
<tr>
<td>lomitapide</td>
<td>C10AX12</td>
</tr>
<tr>
<td>meningococcus A, purified polysaccharides antigen conjugated</td>
<td>J07AH10</td>
</tr>
<tr>
<td>mirabegron</td>
<td>G04BD12</td>
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<tr>
<td>nafcillin</td>
<td>J01CF06</td>
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<tr>
<td>ormeloxifen</td>
<td>G03XC04</td>
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### New ATC 5th level codes (cont.):

<table>
<thead>
<tr>
<th>INN Common name</th>
<th>ATC code</th>
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<tbody>
<tr>
<td>pioglitazone and sitagliptin</td>
<td>A10BD12</td>
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<tr>
<td>ridaforolimus</td>
<td>L01XE19</td>
</tr>
<tr>
<td>rubidium $^{82}$Rb chloride</td>
<td>V09GX04</td>
</tr>
<tr>
<td>simvastatin and fenofibrate</td>
<td>C10BA04</td>
</tr>
<tr>
<td>sitagliptin and simvastatin</td>
<td>A10BH51</td>
</tr>
<tr>
<td>technetium $^{99m}$Tc ethylene-dicysteine</td>
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### ATC code changes:

<table>
<thead>
<tr>
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<th>New ATC</th>
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<tbody>
<tr>
<td>besifloxacin</td>
<td>S01AX23</td>
<td>S01AE08</td>
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<tr>
<td>ciprofloxacin</td>
<td>S01AX13</td>
<td>S01AE03</td>
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<tr>
<td>diamorphine</td>
<td>N02AA09</td>
<td>N07BC06</td>
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<td>droperidol</td>
<td>N01AX01</td>
<td>N05AD08</td>
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<td>gatifloxacin</td>
<td>S01AX21</td>
<td>S01AE06</td>
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<tr>
<td>histrelin</td>
<td>H01CA03</td>
<td>L02AE05</td>
</tr>
<tr>
<td>levofloxacin</td>
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<td>S01AE05</td>
</tr>
<tr>
<td>lomefloxacin</td>
<td>S01AX17</td>
<td>S01AE04</td>
</tr>
<tr>
<td>lopinavir and ritonavir *</td>
<td>J05AE06</td>
<td>J05AR10</td>
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<tr>
<td>moxifloxacin</td>
<td>S01AX22</td>
<td>S01AE07</td>
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<tr>
<td>norfloxacin</td>
<td>S01AX12</td>
<td>S01AE02</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>S01AX11</td>
<td>S01AE01</td>
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<tr>
<td>rivaroxaban</td>
<td>B01AX06</td>
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* New ATC level name (previous name: lopinavir)

### ATC name changes:

<table>
<thead>
<tr>
<th>Previous</th>
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</thead>
<tbody>
<tr>
<td>Other cephalosporins</td>
<td>Other cephalosporins and penems</td>
<td>J01DI</td>
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### New DDDs:

<table>
<thead>
<tr>
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<th>DDD</th>
<th>Unit</th>
<th>Adm.R</th>
<th>ATC code</th>
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</thead>
<tbody>
<tr>
<td>abiraterone</td>
<td>1</td>
<td>g</td>
<td>O</td>
<td>L02BX03</td>
</tr>
<tr>
<td>amifampridine</td>
<td>40</td>
<td>mg</td>
<td>O</td>
<td>N07XX05</td>
</tr>
<tr>
<td>apixaban</td>
<td>5</td>
<td>mg</td>
<td>O</td>
<td>B01AF02</td>
</tr>
<tr>
<td>belatacept</td>
<td>12.5</td>
<td>mg</td>
<td>P</td>
<td>L04AA28</td>
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<tr>
<td>belimimab</td>
<td>25</td>
<td>mg</td>
<td>P</td>
<td>L04AA26</td>
</tr>
<tr>
<td>boceprevir</td>
<td>2.4</td>
<td>g</td>
<td>O</td>
<td>J05AE12</td>
</tr>
<tr>
<td>ciclesonide</td>
<td>0</td>
<td>mg</td>
<td>N</td>
<td>R01AD13</td>
</tr>
<tr>
<td>collagenase clostridium histolyticum</td>
<td>0.9</td>
<td>mg</td>
<td>P</td>
<td>M09AB02</td>
</tr>
<tr>
<td>delavirdine</td>
<td>1.2</td>
<td>g</td>
<td>O</td>
<td>J05AG02</td>
</tr>
<tr>
<td>dextromethorpen, combinations</td>
<td>40</td>
<td>mg</td>
<td>O</td>
<td>N07XX59</td>
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### New DDDs (cont.):

<table>
<thead>
<tr>
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<th>Unit</th>
<th>Adm.R</th>
<th>ATC code</th>
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<td>exenatide</td>
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<td>mg</td>
<td>P depot inj</td>
<td>A10BX04</td>
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<tr>
<td>fidaxomicin</td>
<td>0.4</td>
<td>g</td>
<td>O</td>
<td>A07AA12</td>
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<tr>
<td>histamine dihydrochloride</td>
<td>0.5</td>
<td>mg</td>
<td>P</td>
<td>L03AX14</td>
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<tr>
<td>inosine pranobex</td>
<td>3</td>
<td>g</td>
<td>O</td>
<td>J05AX05</td>
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<tr>
<td>lorazepam</td>
<td>2.5</td>
<td>mg</td>
<td>P</td>
<td>N05BA06</td>
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<tr>
<td>nabiximols</td>
<td>42</td>
<td>mg</td>
<td>SL</td>
<td>N02BG10</td>
</tr>
<tr>
<td>naproxen and esomeprazole</td>
<td>0.5</td>
<td>g²</td>
<td>O</td>
<td>M01AE52</td>
</tr>
<tr>
<td>pyrvinium</td>
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<td>g</td>
<td>O</td>
<td>P02CX01</td>
</tr>
<tr>
<td>retigabine</td>
<td>0.9</td>
<td>g</td>
<td>O</td>
<td>N03AX21</td>
</tr>
<tr>
<td>rifaximin</td>
<td>0.6</td>
<td>g</td>
<td>O</td>
<td>A07AA11</td>
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<tr>
<td>telaprevir</td>
<td>2.25</td>
<td>g</td>
<td>O</td>
<td>J05AE11</td>
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<tr>
<td>tobramycin</td>
<td>0.112</td>
<td>g</td>
<td>Inhal. powder</td>
<td>J01GB01</td>
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<tr>
<td>triptorelin</td>
<td>0.1</td>
<td>mg</td>
<td>P</td>
<td>L02AE04</td>
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<tr>
<td>vinpocetine</td>
<td>15</td>
<td>mg</td>
<td>O</td>
<td>N06BX18</td>
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<tr>
<td>von Willebrand factor</td>
<td>6</td>
<td>TU</td>
<td>P</td>
<td>B02BD10</td>
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</table>

1 expressed as dextromethorphan
2 refers to naproxen

### Herbal medicinal products*

#### New ATC 5th level codes:

<table>
<thead>
<tr>
<th>Name</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agni casti fructus</td>
<td>G02CX03</td>
</tr>
<tr>
<td>Cimicifugae rhizoma</td>
<td>G02CX04</td>
</tr>
</tbody>
</table>

*Assessed and approved by regulatory authorities based on dossiers including efficacy, safety, and quality data (e.g. the well-established use procedure in EU).
Recent Publications,
Information and Events

Evolving threat of antimicrobial resistance

Antimicrobial resistance (AMR) has evolved to become a worldwide health threat and every antibiotic ever developed is now at risk. The evolving threat of antimicrobial resistance: options for action, launched by the World Health Organization (WHO), showcases examples of action taken to slow down drug resistance and preserve the ability of medicine to effectively treat many infectious diseases. The steps taken by governments, health facilities and providers and others are examples of what is recommended in the 2001 WHO Global Strategy for Containment of Antimicrobial Resistance.

Drug resistance causes increased and prolonged illness, a greater risk of complications and higher death rates. Infections which are increasingly resistant to antibiotics are causing a heavy disease burden, particularly in developing countries.

Some examples of a number of successful strategies and measures are highlighted in the book and include:

- In Thailand, the «Antibiotic Smart Use» programme has shown an 18%–46% reduction in antibiotic use.
- A programme targeting pharmacies in Viet Nam and consisting of inspection of prescription-only drugs, education on pharmacy treatment guidelines and group meetings of pharmacy staff resulted in a significant reduction in antibiotic dispensing for acute respiratory infections.
- In Norway, the introduction of effective vaccines in farmed salmon and trout together with improved fish health management reduced the annual use of antimicrobials in farmed fish by 98% between 1987 and 2004.
- In 2010, the University of Zambia School of Medicine revised its undergraduate medical curriculum. The topics of AMR and rational use of medicines were given prominence.


Safety of medicines in sub-Saharan Africa

With an increase in access to new essential medicines in Africa, there is a greater need to monitor and promote safety, quality, and effectiveness of medicines. The burden of adverse events from poor product quality, adverse drug reactions, and medication errors pose great challenges to health care systems, besides the impact on morbidity and mortality. Yet few developing countries have the structures, systems, or resources in place to conduct pharmacovigilance activities, and countries often lack unbiased, evidence-based information to help guide regulatory and patient safety decisions.

Safety of medicines in sub-Saharan Africa: assessment of pharmacovigilance systems and their performance has been developed by the Strengthening Pharmaceutical Systems (SPS) Programme funded by USAID and implemented by Management Sciences for Health (MSH). It provides a comprehensive description...
and analysis of pharmacovigilance systems and their performance in sub-Saharan Africa. The data was compiled in 2011 using more than 400 literature reviews and assessments in 46 sub-Saharan African countries.


International meeting of world pharmacopoeias

In a world of increased globalization, international pharmaceutical standards are becoming increasingly important to safeguard quality and improve access to medicines.

At a meeting hosted by the World Health Organization (WHO) in Geneva in early 2012, representatives from 23 pharmacopoeias and pharmacopeia commissions came together and committed to working towards harmonization and strengthening WHO’s role in developing global standards for the production and testing of medicines.

The meeting has launched greater collaborative work and sharing of information between world pharmacopoeias. Future projects discussed include a new internet-based system for information exchange hosted by WHO, as well as a guide to «good pharmacopoeial practices», currently under development by Argentina, Brazil, the European Pharmacopoeia, India, Japan, Mexico, the Russian Federation, Ukraine, the United Kingdom and the United States Pharmacopeia.


Interagency emergency health kit 2011

UN agencies and international and nongovernmental organizations are increasingly called upon to respond to large-scale emergencies to prevent and manage serious threats to the survival and health of affected populations. Medicines and medical devices have been supplied by relief agencies for decades.

In the 1980s, the World Health Organization (WHO) facilitated a process to encourage the standardization of medicines and medical devices needed in emergencies to allow efficient and effective response to the need for medicines and medical devices. This initial work led to the supply of standard, pre-packed kits that could be kept in readiness to meet priority health needs in emergencies. The concept of the emergency health kit has been adopted by many organizations and national authorities as a reliable, standardized, affordable and quickly available source of the essential medicines and medical devices urgently needed in a disaster situation. Its content is based on the health needs of 10000 people for a period of three months.

The interagency emergency health kit, now in its fourth edition, explains how to use standardized packages of essential medicines, supplies and equipment in such circumstances. The 2011 edition improves the kit content and takes into account the need for mental health care in emergency settings and the special needs of children. It also provides background information on the composition and use of the emergency health kit. Chapter one describes supply needs in emergency situations and is intended as a general introduction for health administrators and field officers. Chapter two explains the selection of medicines and medical devices — renewable and equipment — that are included in the kit, and also provides more technical details intended for prescribers. Chapter three
describes the composition of the kit, which consists of basic and supplementary units.

The annexes provide references to treatment guidelines, sample forms, a health card, guidelines for suppliers, other kits for emergency situations, a standard procedure for importation of controlled medicines, and useful addresses. A feedback form is also included to report on experiences when using the kit and to encourage comments and recommendations on the contents of the kit from distributors and users for consideration when updating the contents.


Guide on estimating pain medication requirements

The World Health Organization (WHO), the International Narcotics Control Board (INCB), and global experts have joined forces to develop a new tool to assist countries to estimate their annual requirements for narcotic drugs for medical purposes. An important treaty requirement of the Single Convention on Narcotic Drugs is that national competent authorities (NCA) should submit estimates annually to the INCB in order to ensure that the amounts of available narcotic drugs and other psychoactive substances are limited to quantities required for medical and scientific purposes.

In order to allow availability of these medications, the WHO and INCB convened a working group to draft a new document called Guide on estimating requirements for substances under international control. It is intended to assist NCAs in calculating requirements for controlled substances. The Guide identifies different methods, explains their potential strengths and weaknesses, and provides an overview of the major issues that need to be considered in order to apply these methods accurately.


Persisting pain in children: treatment guidelines

WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses have recently been published. The guidelines address persisting pain in children caused by conditions such as cancer, HIV/AIDS, sickle-cell disease, burns, trauma, and phantom limb pain.

A new recommendation in the guidelines is a two step approach to treat the child’s pain according to severity: use of a three step ladder is no longer recommended for pain in children. WHO has identified morphine as one of the key medicines necessary to treat chronic pain in children.

Recommendations were developed following a careful and transparent appraisal of available evidence and are presented for the pharmacological treatment of mild, moderate and severe pain.

The Persisting pain in children package contains the WHO guidelines, three brochures targetting physicians and nurses, pharmacists, or policy-makers; a dosing card; two pain scales for children, and a wall chart for waiting rooms.

Consultation Documents

The International Pharmacopoeia

Levonorgestrel and ethinylestradiol tablets

Draft proposal for The International Pharmacopoeia (January 2012). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22 791 4730 or e-mail to schmidt@who.int. Working documents are available for comment at http://www.who.int/medicines.

Category. Contraceptive.

Storage. Levonorgestrel and Ethinylestradiol tablets should be kept in well-closed containers, protected from light.

Labelling. For Levonorgestrel and Ethinylestradiol tablets presented in 21-day or 28-day calendar packs, apply the requirements separately to tablets of each combination of different proportions, by weight, of the active ingredients. Where applicable, disregard any tablets that contain no active ingredient (placebo tablets).

Additional information. Strengths in the current WHO Model List of Essential Medicines: 150 µg Levonorgestrel and 30 µg Ethinylestradiol.

The tablets may be coated.

Requirements

Comply with the monograph for "Tablets".

Definition. Levonorgestrel and ethinylestradiol tablets contain Levonorgestrel and Ethinylestradiol. They contain not less than 90.0% and not more than 110.0% of the amounts of levonorgestrel (C21H28O2) and ethinylestradiol (C20H24O2) stated on the label.

Identity tests

Either tests A, C and D or tests B, 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, using silica gel R1 as the coating substance and a mixture of 70 volumes of cyclohexane R and 30 volumes of acetone R as the mobile phase. Apply separately to the plate 10 µl of each of the following three solutions. For solution (A), to a quantity of the powdered tablets containing about 300 µg of Levonorgestrel and about 60 µg of Ethinylestradiol, add 1 ml of dichloromethane R, shake to dissolve,
centrifuge and use the clear supernatant. For solution (B) use about 300 µg of levonorgestrel RS per ml in dichloromethane R. For solution (C) use about 60 µg of ethinylestradiol RS per ml in dichloromethane R. After removing the plate from the chromatographic chamber, allow it to dry in air. Spray the plate with 4-toluene-sulfonic acid/ethanol TS, and heat at 110 °C for 10 minutes. Examine the chromatogram in ultraviolet light (365 nm).

One of the principal spots in the chromatogram obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B and the other principal spot corresponds to that in the chromatogram obtained with solution C.

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described under test A.1. Examine the chromatogram in daylight.

One of the principal spots in the chromatogram obtained with solution A corresponds in position, appearance and intensity with that obtained with solution B and the other principal spot corresponds to that in the chromatogram obtained with solution C.

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

C. See the method described below under the test for Dextronorgestrel. The retention time of the principal peak in the chromatogram obtained with solution (4) is similar to that in the chromatogram obtained with solution (5).

D. To a quantity of the powdered tablets containing about 750 µg of Levonorgestrel and about 150 µg of Ethinylestradiol, add 10 ml of dichloromethane R, stir thoroughly and filter. To 2 ml of successive filtrate add 2 ml of trinitrophenol alkaline TS1 and allow to stand for 30 minutes; a brownish-yellow color is produced.

**Dissolution**

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 500 ml of polysorbate 80 (~5 µg/ml) VS, and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 15 ml of the dissolution medium through an in-line filter, discarding the first 10 ml of the filtrate [solution (1)].

Determine the concentration in solution (1) by carrying out the test as described under 1.14.4 High-performance liquid chromatography, using the chromatographic conditions given under Assay, method A.

For solution (2) transfer 1 ml of the solution (2) obtained from the Assay, method A to a 100 ml volumetric flask and make up to volume with the dissolution medium.

Operate with a flow rate of 1 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 247 nm for levonorgestrel analysis, and a spectrofluorometric detector for ethinylestradiol analysis with an excitation wavelength of 285 nm and an emission wavelength of 310 nm.

Inject separately 100 µl each of solutions (1) and (2).
Measure the areas of the two principal peaks obtained in the chromatograms from solutions (1) and (2), and calculate the content of levonorgestrel (C21H28O2) and ethinylestradiol (C20H24O2).

**For uncoated tablets.** For each of the six tablets tested, the amounts in solution are not less than 85% of the amount of levonorgestrel and not less than 80% of the amount of ethinylestradiol stated in the label. If for one of the six tablets the amount of levonorgestrel is less than 85% and/or the amount of ethinylestradiol is less than 80%, repeat the test using a further six tablets; the average amounts for all 12 tablets tested are not less than 80% of levonorgestrel and not less than 75% of ethinylestradiol; and no tablet releases less than 65% of levonorgestrel and/or less than 60% of ethinylestradiol.

**For coated tablets.** For each of the six tablets tested, the amounts in solution are not less than 65% of the amounts of levonorgestrel and ethinylestradiol stated in the label. If for one of the six tablets the amounts of levonorgestrel and/or ethinylestradiol are less than 65%, repeat the test using a further six tablets; the average amounts for all 12 tablets tested are not less than 60% of levonorgestrel and ethinylestradiol; and no tablet releases less than 45% of levonorgestrel and ethinylestradiol.

[Note from the Secretariat: A dissolution test using 0.1% sodium dodecyl sulfate R in hydrochloric acid (0.1 mol/l) VS as a medium is under investigation.]

**Dextronorgestrel**

Carry out the chromatographic procedure as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (15 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl group (5 µm). (Hypersil ODS is suitable.) As the mobile phase, use a filtered and degassed solution containing equal volumes of methanol R and gamma-cyclodextrin (∼10 g/l) TS.

Prepare the following solutions in a dissolution solvent prepared by mixing 80 volumes of methanol R and 20 volumes of water R. For solution (1), transfer a quantity of powdered tablets containing about 1.2 mg of Levonorgestrel to a 10-ml volumetric flask. Add about 8 ml of the dissolution solvent, heat in a water-bath at 60 °C for 10 minutes, shaking occasionally. Allow to equilibrate to room temperature, dilute to volume with the dissolution solvent and mix. Filter through a 0.45-µm filter. For solution (2), use 12 µg of norgestrel RS per ml. For solution (3), use 0.12 µg of Levonorgestrel RS per ml. For solution (4), dilute a suitable volume of solution (1) to obtain a concentration of 6.0 µg of Levonorgestrel per ml. For solution (5) use 6.0 µg of levonorgestrel RS per ml.

Operate with a flow rate of 1.5 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 242 nm.

Inject 20 µl of solution (2). The test is not valid unless, in the chromatogram obtained with solution (2), the resolution factor between the two principal peaks (due to levonorgestrel, eluting first and dextronorgestrel) is at least 1.5.

Inject separately 20 µl, each of solutions (1) and (3); and if needed for Identity test C, solutions (4) and (5).
In the chromatogram obtained with solution (1) the area of any peak corresponding
to dextronorgestrel, is not greater than the area of the principal peak in the chromato-
gram obtained with solution (3) (0.1%).

**Assay**

Either method A or B may be applied

A. Weigh and powder 20 tablets. Carry out the test as described under 1.14.4 High-
performance liquid chromatography, using a stainless steel column (25 cm × 4.6 mm)
packed with particles of silica gel, the surface of which has been modified with che-
merically bonded octadecylsilyl group (5 µm). (Hypersil ODS is suitable.) As the mobile
phase, use a solution prepared by mixing 57 volumes of acetonitrile R and 43 volumes
of water R.

Prepare the following solutions using the mobile phase as diluent. For solution (1),
transfer an accurately weighed quantity of the powdered tablets containing about 150
µg of Levonorgestrel and about 30 µg of Ethinylestradiol to a 5-ml volumetric flask.
Add about 4 ml of the mobile phase and shake for 20 minutes, dilute to volume and
mix. Centrifuge and use the clear supernatant. For solution (2), prepare a solution
containing about 30.0 µg of levonorgestrel RS per ml and 6.0 µg of ethinylestradiol RS
per ml.

Operate with a flow rate of 1 ml per minute. As a detector, use an ultraviolet spectro-
photometer set at a wavelength of 215 nm.

Inject separately 50 µl each of solutions (1) and (2). In the chromatogram obtained
with solution (2), the test is not valid unless the resolution factor between the peaks
due to levonorgestrel and ethinylestradiol is at least 2.0.

Measure the areas of the peak responses obtained in the chromatogram from solu-
tions (1) and (2), and calculate the content of levonorgestrel (C21H28O2) and ethiny-
lestradiol (C20H24O2) in the tablets.

B. Use the average of the 10 individual results obtained in the test for Uniformity of
content.

**Uniformity of content**

The tablets comply with the test for 5.1 Uniformity of content for single-dose prepara-
tions, using the following method of analysis.

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

Prepare the following solutions using the mobile phase as diluent. For solution (1),
transfer one tablet to a 5-ml volumetric flask. Add about 4 ml of the mobile phase,
sonicate to disintegrate the tablet and shake for 20 minutes. Centrifuge and use the
clear supernatant. For solution (2) prepare a solution containing about 30.0 µg of levo-
norgestrel RS per ml and 6.0 µg of ethinylestradiol RS per ml.

Inject separately 50 µl each of solutions (1) and (2). In the chromatogram obtained
with solution (2), the test is not valid unless the resolution factor between the peaks
due to levornorgestrel and ethinylestradiol is at least 2.0.
Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of levonorgestrel (C21H28O2) and ethiny-lestradiol (C20H24O2) in each tablet.

*****

New reagents to be added to Ph.Int:

Gamma-cyclodextrin (~10g/l) TS. Dissolve 5.0 g of gamma-cyclodextrin R in 500 ml of water R.

Trinitrophenol, alkaline, TS1. Immediately before use, mix equal volumes of a (~6g/l) solution of trinitrophenol R in ethanol (~750g/l) TS, sodium hydroxide (~70g/l)TS, and a mixture of 52 volumes of ethanol (~750g/l) TS and 48 volumes of water R.

Mefloqui hydrochloridum
Mefloquine hydrochloride

Draft proposal for The International Pharmacopoeia (January 2012).
Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22 791 4730 or e-mail to schmidth@who.int. Working documents are available for comment at http://www.who.int/medicines.

[Note from the Secretariat: following the adoption of the text for Mefloquine tablets in October 2010, it is proposed to revised the monograph for the API accordingly]

C17H16F6N2O,HCl

Relative molecular mass. 414.8

Chemical name. DL-erythro-α-2-piperidyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol monohydrochloride; (R*,S*)-(±)-α-2-piperidyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol monohydrochloride; CAS Reg. No. 51773-92-3.

Description. A white to slightly yellow, crystalline powder.

Solubility. Very slightly soluble in water; freely soluble in methanol R; soluble in ethanol (~750 g/l) TS; sparingly soluble in dichloromethane R.
Category. Antimalarial.

Storage. Mefloquine hydrochloride should be kept in a tightly closed container, protected from light.

Additional information. Mefloquine hydrochloride may exhibit polymorphism. It melts at about 260 °C, with decomposition.

Requirements

Mefloquine hydrochloride contains not less than 99.0% and not more than 101.0% of C17H16F6N2O,HCl, calculated with reference to the anhydrous substance.

Identity tests

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

A. 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 mefloquine hydrochloride RS or with the reference spectrum of mefloquine hydrochloride. If the spectra thus obtained are not concordant, repeat the test using the residues obtained by separately dissolving the test substance and mefloquine hydrochloride RS in methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from mefloquine hydrochloride RS.

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

B.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 70 volumes of toluene R, 30 volumes of ethanol R and 2 volumes of 25% ammonia solution R as the mobile phase. Apply separately to the plate 10 μl of each of the following two solutions in methanol R. For solution (A) use 10 mg of the test substance per ml. For solution (B) use 10 mg of mefloquine hydrochloride 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 spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test B.1 but using silica gel R5 as the coating substance. Stain the plate with iodine vapours. Examine the chromatogram in daylight.

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

C. The absorption spectrum (1.6) of a 54 μg/ml solution in methanol R, when observed between 250 nm and 290 nm, exhibits one maximum at about 283 nm.

D. A 50 mg/ml solution yields reaction B described under 2.1 General identification tests as characteristic of chlorides.
[Note from the Secretariat: similarly as for Mefloquine tablets]

- former Test B has been replaced by a TLC method;
- former Test C and D have been replaced by a UV method.]

Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 3; determine the heavy metals content according to Method A; not more than 20 μg/g.

[Note from the Secretariat: the former test for Solution in methanol has been deleted in this proposal to take into account current practice.]

Sulfated ash. Not more than 1.0 mg/g.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using 1.0 g of the substance; the water content is not more than 30 mg/g.

Related substances
Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyle groups (5 μm). (Luna® was found suitable.)

As the mobile phase, use a mixture of 22 volumes of methanol R, 38 volumes of acetonitrile R and 40 volumes of buffer pH 3.5 prepared as follows: dissolve 13.6 g potassium dihydrogen phosphate in about 900 ml of water R, adjust the pH to 3.5 by addition of 10% phosphoric acid and dilute to 1000 ml.

Prepare the following solutions in the mobile phase. For solution (1) use about 2.2 mg of the test substance per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 4.4 μg of Mefloquine hydrochloride per ml. For solution (3) use about 0.22 mg of mefloquine hydrochloride RS and about 0.04 mg of sulfadoxine R per ml.

Operate with a flow rate of 1.5 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of about 283 nm.

Inject 20 μl of solution (3). The test is not valid unless the resolution between the two principal peaks is at least 5.

Inject separately 20 μl each of solutions (1) and (2). Record the chromatograms for about 10 times the retention time of mefloquine.

In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to mefloquine (retention time about 3.9 minutes): impurity A about 0.9, impurity C about 3.6 and impurity B about 7.4.

In the chromatogram obtained with solution (1) the area of any peak corresponding to impurity A, is not greater than the area of the principal peak in the chromatogram.
obtained with solution (2) (0.2%) and the area of any other peak, apart from the principal peak, is not greater than 0.5 times the area of the peak in the chromatogram obtained with solution (2) (0.1%). The sum of the areas of all peaks, other than the peak due to mefloquine, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%). Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

**Note from the Secretariat:** The former specific test for Ethanol, methanol and acetone has been deleted in this proposal. The possibility to include under the Supplementary section of the Ph.Int., a general text on residual solvents for APIs is under review.

**Assay**

Dissolve about 0.31 g, accurately weighed, in 70 ml of glacial acetic acid R1, add 5 ml of mercuric acetate/acetic acid TS, and titrate with perchloric acid (0.1 mol/l) VS as described under 2.6 Non-aqueous titration, Method A.

Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 41.48mg of C17H16F6N2O, HCl.

**Note from the Secretariat:** due to the toxicity of mercuric acetate/acetic acid TS, replacement of this reagent is under review.

**Impurities**

**Note from the Secretariat:** this section has been transferred from the Mefloquine tablets monograph. The latter should have instead a cross-reference to this API monograph.

A. (RS)-[2,8-bis(trifluoromethyl)quinolin-4-yl][2RS]-piperidin-2-yl]methanol (threo-mefloquine) and enantiomer

B. (RS)-[2,8-bis(trifluoromethyl)quinolin-4-yl][pyridin-2-yl]methanone
C. (RS)-[2,8-bis(trifluoromethyl)quinolin-4-yl][pyridin-2-yl]methanol

New reagents to be added to Ph.Int.

** ****

**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).

**Sulfadoxine R.** N 1-(5,6-Dimethoxy-4-pyrimidinyl)sulfanilamide; 4-amino-N-(5,6-dimethoxy-4-pyrimidinyl)benzenesulfonamide; C12H14N4O4S

A commercially available reagent of suitable grade.

**Description.** A white or creamy white, crystalline powder.

**Solubility.** Very slightly soluble in water; slightly soluble in ethanol (~750 g/l) TS and in methanol R; practically insoluble in ether R.

**Fluconazoli**

**Fluconazole**

Draft proposal for The International Pharmacopoeia (April 2012). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22 791 4730 or e-mail to schmidt@who.int. Working documents are available for comment at http://www.who.int/medicines.
Relative molecular mass. 306.3

Chemical name. 2-(2,4-Difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol; CAS Reg. No.86386-73-4.

Description. A white or almost white, hygroscopic, crystalline powder.

Solubility. Slightly soluble in water, freely soluble in methanol, soluble in acetone. It shows polymorphism.

Category. Antifungal.

Storage. Fluconazole should be kept in a tightly closed container, stored below 30°C.

Requirements

Definition. Fluconazole contains not less than 99.0% and not more than 101.0% of C13H12F2N6O, calculated with reference to the dried substance.

Identity tests

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

A. 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 Fluconazole RS or with the reference spectrum of fluconazole. If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in the minimum volume of methylene chloride R, evaporate to dryness on a water-bath and record new spectra using the residues.

B. 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 80 volumes of dichloromethane R, 20 volumes of methanol R, and 1 volume of concentrated-ammonia R solution as the mobile phase. Apply separately to the plate 20 μl of each of the following three solutions in methanol R. For solution (A) use 10 mg of Fluconazole per ml. For solution (B) use 10 mg of fluconazole RS per ml. For solution (C) use a solution containing 10 mg of fluconazole RS per ml and 10 mg of fluconazole impurity A 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 spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid, unless the chromatogram obtained with solution (C) shows two clearly separated spots.

C. The absorption spectrum (1.6) of a 200 μg/ml solution in ethanol R, exhibits maxima at about 261 nm and 267 nm, and a minimum at 264 nm.

Clarity and colour of solution. A solution of 1.0 g in 20 ml of methanol R is clear and colourless.
Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 3; determine the heavy metals content according to Method A; not more than 10 μg/g.

Sulfated ash (2.3). Not more than 1.0 mg/g, using Method B and a platinum crucible.

Loss on drying. Dry to constant weight at 105 °C; it loses not more than 5 mg/g.

Related substances
Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecysilyl groups (5 μm). As the mobile phase, use a mixture of 86 volumes of a (0.63 g/l) solution of ammonium formate R and 14 volumes of acetonitrile R.

Prepare the following solutions in the mobile phase. For solution (1) use 10 mg of Fluconazole per ml. For solution (2) dilute 5 volumes of solution (1) to 100 volumes, then dilute 1 volume of this solution to 10 volumes. For solution (3) use 0.5 mg of fluconazole for peak identification RS (containing impurity A) per ml. For solution (4) use 0.03 mg of fluconazole impurity B RS per ml. For solution (5) use 0.1 mg of fluconazole impurity C RS per ml. To 1.0 ml of this solution add 1.0 ml of solution (1) and dilute to 10.0 ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 260 nm.

Inject separately 20 μl each of solutions (1), (2), (3), (4) and (5). Record the chromatograms to 3.5 times the retention time of fluconazole and identify the impurity peaks. The peaks are eluted at the following relative retentions with reference to fluconazole (retention time about 11 minutes): impurity B about 0.4; impurity A about 0.5; impurity C about 0.8. The test is not valid, unless in the chromatogram obtained with solution (5), the resolution between the peaks due to impurity C and to fluconazole is at least 1.5.

In the chromatogram obtained with solution (1), the area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%); the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.3%); the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%); the area of any other impurity peak is not greater than 0.2 times 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 peak due to fluconazole is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Assay
Dissolve about 0.1 g, accurately weighed, in 50 ml of anhydrous acetic acid R and titrate with perchloric acid (0.1 mol/l) VS as described under 2.6 Non-aqueous titration, Method A, determining the end-point potentiometrically.
Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 15.32 mg of C13H12F2N6O.

**Impurities**

A. (2RS)-2-(2,4-difluorophenyl)-1-(1H,1,2,4-triazol-1-yl)-3-(4H-1,2,4-triazol-4-yl)propan-2-ol,

B. 2-[2-fluoro-4-(1H,1,2,4-triazol-1-yl)phenyl]-1,3-bis(1H,1,2,4-triazol-1-yl)propan-2-ol,

C. 1,1’-(1,3-phenylene)di-1H-1,2,4-triazole,
D. 2-(4-fluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol,

E. 1-[(6RS)-4,6-difluoro-6-(1H-1,2,4-triazol-1-yl)cyclohexa-1,4-dienyl]ethanone,

F. R=OH:(2RS)-2-(2,4-difluorophenyl)-3-(1H-1,2,4-triazol-1-yl) propan-2-diol,
H. R=Br:(2RS)-1-bromo-2-(2,4-difluorophenyl)-3-(1H-1,2,4-triazol-1-yl) propan-2-ol,

G.[3-][(2RS)-2-(2,4-difluorophenyl)oxiran-2-yl]methyl[1H-1,2,4-triazol-1-yl]methanesulfonic acid,
I. 4-amino-1-[(2RS)-2-(2,4-difluorophenyl)-2-hydroxy-3(1H-1,2,4-triazol-1-yl)propyl]-4H-1,2,4-triazolium.

[Note from Secretariat: chemical names and structures to be confirmed.]

Fluconazoli compressi
Fluconazole capsules

Draft proposal for The International Pharmacopoeia (April 2012). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22 791 4730 or e-mail to schmidth@who.int. Working documents are available for comment at http://www.who.int/medicines.

Category. Antifungal.

Storage. Fluconazole capsules should be kept in a tightly closed container and stored at a temperature not exceeding 30 °C.


Requirements

Comply with the monograph for «Capsules».

Definition. Fluconazole capsules contain Fluconazole. They contain not less than 90.0% and not more than 110.0% of the amount of fluconazole (C13H12F2N6O) stated on the label.

Identity tests

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

A. 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 80 volumes of dichloromethane R, 20 volumes of methanol R, and 1 volume of concentrated-ammonia R solution as the mobile phase. Apply separately to the plate 10 μl of each of the following three solutions in methanol R. For solution (A) shake a quantity of the contents of the
capsules containing about 100 mg of Fluconazole with 10 ml of methanol R, filter, and use the clear filtrate. For solution (B) use 10 mg of fluconazole RS per ml. For solution (C) use a mixture of 10 mg of fluconazole RS and 10 mg of fluconazole impurity A 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 spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid, unless the chromatogram obtained with solution (C) shows two clearly separated spots.

B. See the test described below under Assay 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. To a quantity of the contents of the capsules containing 2 mg of Fluconazole, add 10 ml of ethanol R, shake and filter. The absorption spectrum (1.6) of the solution exhibits maxima at 261 nm and 267 nm, and a minimum at 264 nm.

**Related substances**

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given below under Assay. Prepare the following solutions in the mobile phase. For solution (1) use an amount of the mixed contents of 20 capsules to produce a solution containing 10 mg of Fluconazole per ml. For solution (2) dilute 5 volumes of solution (1) to 100 volumes, then dilute 1 volume of this solution to 10 volumes. For solution (3) use 0.5 mg of fluconazole for peak identification RS (containing impurity A) per ml. For solution (4) use 0.03 mg of fluconazole impurity B RS per ml. For solution (5) use 0.1 mg of fluconazole impurity C RS per ml. To 1.0 ml of this solution, add 1.0 ml of solution (1) and dilute to 10.0 ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 260 nm.

Inject separately 20 μl each of solutions (1), (2), (3), (4) and (5). Record the chromatograms to 3.5 times the retention time of Fluconazole and identify the impurity peaks. The peaks are eluted at the following relative retentions with reference to fluconazole (retention time about 11 minutes): impurity B about 0.4; impurity A about 0.5; impurity C about 0.8. The test is not valid, unless in the chromatogram obtained with solution (5), the resolution between the peaks due to impurity C and to fluconazole is at least 1.5.

In the chromatogram obtained with solution (1), the area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%); the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.3%); the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%); the area of any other impurity peak is not greater than 0.2 times 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 Fluconazole peak is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).
Dissolution test

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 500 ml (for strength 50 mg capsules) of hydrochloric acid (0.1 mol/l) TS or using 1000 ml (for strength 200 mg capsules) hydrochloric acid (0.1 mol/l) TS and rotating the paddle at 100 revolutions per minute. At 45 minutes withdraw a sample of about 10 ml of the medium through a suitable 0.45 μm filter. Measure the absorbance (1.6) of a 1 cm layer of the successive filtrate, suitably diluted if necessary, at the maximum at 261 nm. Measure the absorbance (1.6) at the maximum at about 261 nm of a reference solution containing 0.1 mg of fluconazole RS per ml in the dissolution medium, using the same solution as the blank.

For each of the six capsules tested, calculate the total amount of fluconazole (C13H12F2N6O) in the medium. The amount in solution for each capsule is not less than 80% of the amount declared on the label. If the amount obtained for one of the six capsules is less than 80%, repeat the test using a further six tablets the average amount for all 12 capsules tested is not less than 75% and no capsule releases less than 60%.

Assay

Either test A or B may be applied.

A. Mix the contents of 20 capsules and transfer a quantity containing about 50 mg of Fluconazole, accurately weighed, to a 10 ml volumetric flask, and dilute to volume with hydrochloric acid (0.1 mol/l) TS. Shake to dissolve, filter a portion of this solution through a 0.45 μm filter and dilute 10 ml of the successive filtrate to 25 ml with the same solution. Measure the absorbance of a 1 cm layer at the maximum at about 261 nm.

Calculate the percentage content of fluconazole (C13H12F2N6O) using as reference a solution containing 0.2 mg of fluconazole RS per ml of hydrochloric acid (0.1 mol/l) TS prepared and examined in the same manner.

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5μm). Capcell Pak® C18 MGII (4.6×250 mm, 5 μm) has been found suitable. As the mobile phase, use a mixture of 86 volumes of a (0.63 g/l) solution of ammonium formate R and 14 volumes of acetonitrile R.

Prepare the following solutions in the mobile phase. For solution (1) use an amount of the mixed contents of 20 capsules to produce a solution containing 0.5 mg of Fluconazole per ml and filter. For solution (2) use 0.5 mg of fluconazole RS per ml. For solution (3) use a solution containing 0.01 mg of fluconazole impurity C RS per ml and 1 mg of fluconazole RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 260 nm.

Inject separately 20 μl of each of solutions (1), (2) and (3). The test is not valid, unless in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity C and to fluconazole is at least 1.5.
Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the percentage content of fluconazole (C13H12F2N6O) in the capsules.

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**Fluconazoli injectio**  
**Fluconazole injection**

Draft proposal for *The International Pharmacopoeia* (April 2012). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22 791 4730 or e-mail to schmidth@who.int. Working documents are available for comment at http://www.who.int/medicines.

**Description.** A clear, colourless solution.

**Category.** Antifungal.

**Storage.** Fluconazole injection should be kept in a tightly closed container, stored at controlled room temperature and protected from light.

Additional information. Strength in the current WHO Model list of Essential Medicines: 2 mg/ml in vial.

**Requirements**

Complies with the monograph for «Parenteral preparations».

**[Note from Secretariat: Some of the Ph.Int. monographs for parenterals have the following general requirements statement: “Comply with the monograph for «Parenteral preparations» and with 5.6 Test for extractable volume for parenteral preparations, 3.4 Test for bacterial endotoxins, and 5.7 Visual inspection of particulate matter in injectable preparations.”**

In October 2011, the Expert Committee adopted the following PDG harmonized texts:

- 3.2 Test for sterility,
- 3.4 Test for bacterial endotoxins,
- 5.6 Extractable volume for parenteral preparations, and  
- 5.7 Test for particulate contamination.

As a consequence, it was recommended that the general monograph on Parenteral preparations be revised in order to make these new/revised tests mandatory for these dosage forms. A revision proposal for the general monograph on Parenteral preparations is currently under elaboration where the compliance to these tests is now invoked. It is, therefore, no longer needed to mention these tests in individual monographs, unless specific limits apply.

**Definition.** Fluconazole injection is a sterile solution of Fluconazole in water for injections.
The solution is sterilized by a suitable method (see 5.8 Methods of sterilization).

Fluconazole injection contains not less than 90.0% and not more than 110.0% of the amount of fluconazole (C13H12F2N6O) stated on the label.

**Identity tests**

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

A. 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 80 volumes of dichloromethane R, 20 volumes of methanol R, and 1 volume of concentrated-ammonia R solution as the mobile phase. Apply separately to the plate 20 μl of each of the following three solutions. For solution (A) use the injection as the resulting solution. For solution (B) use 2 mg of fluconazole RS per ml in methanol R. For solution (C) use a mixture of 2 mg of fluconazole RS per ml and 2 mg of fluconazole impurity A RS per ml in methanol R. 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 spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The test is not valid, unless the chromatogram obtained with solution (C) shows two clearly separated spots.

B. See the test described below under Assay. 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. Dilute a volume of the injection containing 2 mg of Fluconazole to 10 ml with water R, the absorption spectrum (1.6) of the resulting solution exhibits maxima at 261 nm and 267 nm, and a minimum at 264 nm.

**pH value** (1.3). pH of the injection, 4.0-6.0.

**Related substances**

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given below under Assay. Prepare the following solutions in the mobile phase. For solution (1) use the injection. For solution (2) dilute 5 volumes of solution (1) to 100 volumes, then dilute 1 volume of this solution to 10 volumes. For solution (3) use 0.5 mg of fluconazole for peak identification RS (containing impurity A) per ml. For solution (4) use 0.006 mg of fluconazole impurity B RS per ml. For solution (5) use 0.02 mg of fluconazole impurity C RS per ml. To 1.0 ml of this solution, add 1.0 ml of solution (1) and dilute to 10.0 ml. For solution (6) use 1 μg of fluconazole RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 260 nm.

Inject separately 20 μl each of solutions (1), (2), (3), (4), (5) and (6). Record the chromatograms to 3.5 times the retention time of fluconazole and identify the impurity peaks. The peaks are eluted at the following relative retentions with reference to fluconazole (retention time about 11 minutes): impurity B about 0.4; impurity A about 0.5; impurity C about 0.8. The test is not valid, unless in the chromatogram obtained with
solution (5), the resolution between the peaks due to impurity C and to fluconazole is at least 1.5; the test is also not valid if the signal-to-noise ratio for solution (6) is at least 10.

In the chromatogram obtained with solution (1), the area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%); the area of any peak corresponding to impurity B is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.3%); the area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%); the area of any other impurity peak is not greater than 0.2 times 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 fluconazole peak is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

**Assay**

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5μm). Capcell Pak® C18 MGII (4.6×250 mm, 5 μm) has been found suitable.

As the mobile phase, use a mixture of 86 volumes of a (0.63 g/l) solution of ammonium formate R and 14 volumes of acetonitrile R.

Prepare the following solutions in the mobile phase. For solution (1) dilute an accurately measured volume of the injection containing about 5 mg of Fluconazole to 10 ml. For solution (2) use 0.5 mg of fluconazole RS per ml. For solution (3) use a solution containing 0.01 mg of fluconazole impurity C RS per ml and 1 mg of fluconazole RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 260 nm.

Inject separately 20 μl of each of solutions (1), (2) and (3). The test is not valid, unless in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity C and to fluconazole is at least 1.5.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the percentage content of fluconazole (C13H12F2N6O) in the injection.

**Bacterial endotoxins.** Carry out the test as described under 3.4 Test for bacterial endotoxins, using Method A; contains not more than 0.416 IU of endotoxin RS per mg of Fluconazole.

*[Note from the Secretariat: in accordance with the revised test 3.4 Bacterial Endotoxins adopted in October 2011 (harmonized text from PDG), the specific method to be used when carrying out the test is now mentioned (gel-clot, turbidimetric technique or chromogenic techniques).]*
Sulfamethoxazoli et trimethoprими infusio intraveno
Sulfamethoxazole and trimethoprim intravenous infusion

Draft proposal for The International Pharmacopoeia (April 2012). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22 791 4730 or e-mail to schmith@who.int. Working documents are available for comment at http://www.who.int/medicines.

[Note from the Secretariat: This draft text is proposed for inclusion in Ph.Int. in the context of a collaboration between WHO and the Medicines and Healthcare Products Regulatory Agency of the United Kingdom of Great Britain and Northern Ireland (MHRA) hosting The British Pharmacopoeia (BP), on which this text is based. Use of «injection» or «infusion» to define this type of dosage form would need to be harmonized with either the WHO Model List of Essential Medicines where the term “injection” is used for this product, or with the existing monograph of a similar dosage form in the Ph.Int. (see Zidovudine intravenous infusion).]

Category. Antibacterials.

Requirements

Complies with the monograph for “Parenteral preparation”.

Definition. Sulfamethoxazole and Trimethoprim intravenous infusion is a sterile solution of Sulfamethoxazole and Trimethoprim in glucose or sodium chloride intravenous infusions. It is prepared immediately before use by diluting Sulfamethoxazole and Trimethoprim sterile concentrate with a 5% glucose infusion or a 0.9% sodium chloride intravenous infusion.

Sulfamethoxazole and trimethoprim sterile concentrate

Description. A colourless or slightly yellow solution.

Storage: Sulfamethoxazole and Trimethoprim sterile concentrate should be kept in tightly closed, single-dose, light-resistant containers, preferably of Type I glass.

[Note from the Secretariat: The BP monograph recommends the storage of the infusion in a “Type I glass container”; however, glass container categories are not described in Ph.Int. Moreover, as described in BP (Appendix XIX B refers – Glass containers for Pharmaceutical use): “Type I glass containers are suitable for most preparations whether or not for parenteral use”.

As this type of glass container is in common use and does not have particular characteristics that would need to be specified in this monograph, it is proposed to omit this information and to mention the general term “glass container” instead.]

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

80 mg per ml Sulfamethoxazole, 16 mg per ml Trimethoprim in 5 ml ampoule
80 mg per ml Sulfamethoxazole, 16 mg per ml Trimethoprim in 10 ml ampoule
Strengths in the current WHO Model List of Essential Medicines for Children:

80 mg per ml Sulfamethoxazole, 16 mg per ml Trimethoprim in 5 ml ampoule
80 mg per ml Sulfamethoxazole, 16 mg per ml Trimethoprim in 10 ml ampoule.

Requirements

Comply with the monograph for “Parenteral preparations”.

Definition. Sulfamethoxazole and Trimethoprim sterile concentrate is a sterile solution of Sulfamethoxazole and Trimethoprim in water for injections, which, when diluted with a 5% glucose intravenous infusion or a 0.9% sodium chloride intravenous infusion, is suitable for intravenous infusion.

The solution is sterilized by a suitable method (see 5.8 Methods of sterilization).

Sulfamethoxazole and Trimethoprim sterile concentrate contains not less than 90.0% and not more than 110.0% of the amounts of Sulfamethoxazole (C10H11N3O3S) and Trimethoprim (C14H18N4O3) stated on the label.

[Note from the Secretariat: It is intended to develop Ph.Int. monographs for Glucose intravenous infusion and Sodium chloride intravenous infusion.]

Identity tests

Either tests A and D 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 100 volumes of dichloromethane R, 10 volumes of methanol R and 5 volumes of dimethylformamide R as the mobile phase. Apply separately to the plate 5 μl of each of the following two solutions in methanol R. For solution (A) evaporate to dryness a volume of the concentrate containing about 0.16 g of Sulfamethoxazole, shake the residue with 8 ml of methanol R and filter. For solution (B) use 20 mg of sulfamethoxazole RS and 4 mg of trimethoprim 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 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 silica gel R5 as the coating substance and the conditions described above under test A.1. Spray the plate with potassium iodobismuthate TS2 solution.

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

B. Add drop wise to 75 ml of hydrochloric acid (~3.65 g/l) TS a volume of the concentrate containing about 0.8 g of Sulfamethoxazole, stirring continuously. Allow the
suspension to stand for 5 minutes and filter through a sintered-glass filter. Wash the residue with 10 ml of water R, recrystallize from ethanol (~750 g/l) TS and dry at 105 °C. Dissolve the residue in the minimum volume of sodium carbonate (~50 g/l) TS, add hydrochloric acid (~36.5 g/l) TS drop wise until precipitation is complete, filter, wash the residue sparingly with water R and dry at 105 °C. The infrared absorption spectrum of the residue is concordant with the reference spectrum of sulfamethoxazole RS.

C. To a volume of the concentrate containing about 80 mg of Trimethoprim add 30 ml of sodium hydroxide (~4 g/l) TS and extract with two quantities of 50 ml of dichloromethane R. Wash the combined extracts with two quantities of 10 ml of sodium hydroxide (~4 g/l) TS and then with 10 ml of water R. Shake with 5 g of anhydrous sodium sulfate R, filter and evaporate the filtrate to dryness. Carry out the test as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum of the residue is concordant with the spectrum obtained from trimethoprim RS or with the reference spectrum of Trimethoprim.

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

pH value (1.13). pH of the solution, 9.5 – 11.0

Bacterial endotoxins. Carry out the test described under 3.4 Test for bacterial endotoxins. Dilute the sterile concentrate with water BET to obtain a solution containing 1 mg of Trimethoprim and 5 mg of Sulfamethoxazole per ml (solution A). Solution A contains not more than 0.5 IU per ml.

Related substances

Trimethoprim-related substances. Carry out the test as described under 1.14.1. Thin-layer chromatography, using silica gel R4 as the coating substance and a mixture of 97 volumes of chloroform R, 7.5 volumes of methanol R, and 1 volume of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 10 µl of each of the following three solutions. For solution (A), transfer an accurately measured volume of concentrate, containing about 48 mg of Trimethoprim and 240 mg of Sulfamethoxazole, to a glass-stoppered, 50 ml centrifuge tube. Add 15 ml of hydrochloric acid (~2.19 g/l) TS, and mix. Add 15 ml of dichloromethane R, shake for 30 seconds, and centrifuge for 3 minutes. Transfer the supernatant layer to a 125-ml separator. Extract the dichloromethane layer in the centrifuge tube with 15 ml of hydrochloric acid (~2.19 g/l) TS, centrifuge and add the extract to the separator. Add 2 ml of sodium hydroxide (~100 g/l) TS to the solution in the separator, and extract with three 20 ml portions of dichloromethane R, collecting the organic layer in a 125 ml conical flask. Evaporate the dichloromethane under a stream of nitrogen to dryness. Dissolve the residue in 1 ml of a mixture of equal volumes of dichloromethane R and methanol R (solvent mixture). For solution (B) use 48 mg of sulfamethoxazole RS per ml of the solvent mixture. For solution (C), dilute an accurately measured volume of solution B with the solvent mixture to obtain a solution of 240 µg per ml. After removing the plate from the chromatographic chamber, allow it dry in air, spray with ferric chloride/potassium ferricyanide TS1 and examine the chromatogram in ultraviolet light (254 nm).

Trimethoprim produces a spot at about RF 0.5, and the trimethoprim degradation product produces a spot at about RF 0.6 to 0.7. Any spot from solution A at about RF 0.6
to 0.7 is not greater in size and intensity than the spot produced by solution C (0.5%). Disregard any spots due to concentrate excipients at about RF 0.1.

**Sulfamethoxazole-related substances.** Carry out the test as described under 1.14.1. Thin-layer chromatography, using silica gel R5 as the coating substance. Prepare an ethanol-methanol solution by mixing 95 volumes of dehydrated ethanol R and 5 volumes of methanol R. As the mobile phase, use a mixture of 30 volumes of ethanol-methanol solution, 30 volumes of heptane R, 30 volumes of dichloromethane R and 10 volumes of glacial acetic acid R. Prepare an ammonium hydroxide solution by diluting 1 ml of ammonia (~ 260 g/l) TS in the ethanol-methanol solution, and dilute to 100 ml with the same solution. Apply separately to the plate 10 µl of each of the following five solutions. For solution (A), transfer an accurately measured volume of concentrate, containing about 32 mg of Trimethoprim and 160 mg of Sulfamethoxazole, to an evaporating dish. Evaporate the sample to dryness using a steam bath. Reconstitute the residue with 16 ml of ammonium hydroxide solution. For solution (B) use 10 mg of sulfamethoxazole RS per ml of ammonium hydroxide solution. For solution (C) use 0.05 mg of sulfanilamide RS per ml of ammonium hydroxide solution. For solution (D) use 0.03 mg of sulfanilic acid RS per ml of ammonium hydroxide solution. For solution (E) dissolve 10 mg of sulfamethoxazole RS in 1 ml of a solution containing 0.05 mg of sulfanilamide RS and 0.03 mg of sulfanilic acid RS per ml of ammonium hydroxide solution. After removing the plate from the chromatographic chamber, allow it dry in air, spray with 4-dimethylaminobenzaldehyde TS7, allow the plate to stand for 15 minutes and examine the chromatogram.

Any spots corresponding to sulfanilamide and sulfanilic acid in the chromatogram obtained with solution A are not greater in size or intensity than the spots obtained with solution C (0.5%) and solution D (0.3%) respectively. The test is not valid unless the chromatogram obtained with solution (E) shows three clearly separated principal spots.

**Assay**

Either method A or methods B and C may be applied.

A. 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 base-deactivated silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm). Hypersil BDS C18 has been found suitable. As the mobile phase, use a solution prepared as follows: mix 1400 ml of water R, 400 ml of acetonitrile R, and 2.0 ml of triethylamine R in a 2000-ml volumetric flask. Allow to equilibrate to room temperature, and adjust with acetic acid (~10 g/l) TS to pH 5.9. Dilute to volume with water R, and filter through a 0.45-µm membrane.

Prepare the following solutions. For solution (1) transfer an accurately measured volume of the concentrate containing about 80 mg of Sulfamethoxazole into a 50-ml volumetric flask. Add methanol R to volume and mix. Transfer 5.0 ml of this solution to a 50-ml volumetric flask, dilute with the mobile phase to volume, mix and filter. For solution (2), use 0.32 mg of trimethoprim RS and 1.60 mg of sulfamethoxazole RS per ml of methanol R. Dilute 5.0 ml of this solution to 50.0 ml with the mobile phase.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm.
Inject separately 20 µl each of solutions (1) and (2) and record the chromatogram for 1.5 times the retention time of sulfamethoxazole. The test is not valid unless the resolution factor between the peaks due to sulfamethoxazole and to trimethoprim is at least 5.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of Sulfamethoxazole (C10H11N3O3S) and Trimethoprim (C14H18N4O3) in the tablets.

B. To an accurately measured volume of the concentrate containing about 48 mg of Trimethoprim, add 30 ml of sodium hydroxide (~4 g/l) TS and extract with four quantities of 50 ml of dichloromethane R, washing each extract twice with a quantity of 10 ml of sodium hydroxide (~4 g/l) TS. Combine the dichloromethane extracts and extract with four quantities of 50 ml of acetic acid (~60 g/l) TS. Wash the combined aqueous extracts with 5 ml of dichloromethane R and dilute to 250.0 ml with acetic acid (~60 g/l). To 10 ml of this solution, add 10 ml of acetic acid (~60 g/l), dilute to 100.0 ml with water R. Measure the absorbance of the resulting solution at the maximum at 271 nm. Calculate the amount of trimethoprim (C14H18N4O3) using the absorptivity value of 20.4 (= 204).

C. To an accurately measured volume of the concentrate containing about 0.4 g of Sulfamethoxazole add 60 ml of water R and 10 ml of hydrochloric acid (~420 g/l) TS. Add 3 g of potassium bromide R, cool in ice and titrate slowly with sodium nitrite (0.1 mol/l) VS, stirring constantly and determining the end-point potentiometrically.

Each ml of sodium nitrite (0.1 mol/l) VS is equivalent to 25.33 mg of Sulfamethoxazole (C10H11N3O3S).

*****

New reagents needed to be added to Ph.Int.:

**Acetic acid (~10 g/l) TS**
Acetic acid (~300 g/l) TS, diluted with water to contain about 10 g of C2H4O per litre.

**Hydrochloric acid (~3.65 g/l) TS**
Hydrochloric acid (~250 g/l) TS, dilute with water to contain 3.65 g of HCl in 1000 ml.

**Hydrochloric acid (~2.19 g/l) TS**
Hydrochloric acid (~250 g/l) TS, dilute with water to contain 2.19 g of HCl in 1000 ml.

**Hydrochloric acid (~36.5 g/l) TS**
Hydrochloric acid (~250 g/l) TS, dilute with water to contain 36.5 g of HCl in 1000 ml.

**Sodium hydroxide (~ 4 g/l) TS**
A solution of sodium hydroxide R containing about 4 g/l of NaOH (approximately 0.1 mol/l).

**Sodium hydroxide (~ 100 g/l) TS**
A solution of sodium hydroxide R containing about 100 g/l of NaOH (approximately 2.5 mol/l).
Ferric chloride / potassium ferricyanide TS1
Procedure. Dissolve 2 g of ferric chloride R and 0.5 g of potassium ferricyanide R in sufficient water to produce 20 ml.

Note. Ferric chloride / potassium ferricyanide TS2 must be freshly prepared.

4-Dimethylaminobenzaldehyde TS7
Dissolve 0.1 g of 4-dimethylaminobenzaldehyde R in 1 ml of hydrochloric acid (~420 g/l) TS, dilute with ethanol (~750 g/l) to produce 100 ml.

Sulfamethoxazole et trimethoprimi solutionum peroralum
Sulfamethoxazole and trimethoprim oral suspension

Draft proposal for The International Pharmacopoeia (April 2012). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22 791 4730 or e-mail to schmidth@who.int. Working documents are available for comment at http://www.who.int/medicines.

Category. Antibacterials.

Storage. The oral suspension should be kept in a tightly closed container, protected from light.

Additional information. Strength in the current WHO Model List of Essential Medicines: 200 mg Sulfamethoxazole, 40 mg Trimethoprim per 5 ml. Strength in the current WHO Model List of Essential Medicines for Children: 200 mg Sulfamethoxazole, 40 mg Trimethoprim per 5 ml.

Requirements
Complies with the monograph for “Liquid preparations for oral use”.

Definition. Sulfamethoxazole and Trimethoprim oral suspension is a suspension containing Sulfamethoxazole and Trimethoprim in a suitable vehicle which may be flavoured. The oral suspension contains not less than 90.0% and not more than 110.0% of Sulfamethoxazole (C10H11N3O3S) and Trimethoprim (C14H18N4O3) stated on the label.

Identity tests
Either test A or B may be applied. Test C may be applied for identification of Trimethoprim.

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 100 volumes of dichloromethane R, 10 volumes of methanol R and 5 volumes of dimethylformamide R as the mobile phase. Apply separately to the plate 5 µl of each of the following two solutions. For solution (A), add 20 ml of methanol R to 5 ml of the oral suspension, mix,
shake with 10 g of anhydrous sodium sulfate R, centrifuge and use the supernatant liquid. For solution (B) use 20 mg of sulfamethoxazole RS and 4 mg of trimethoprim RS per ml methanol R. 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 spots obtained with solution A correspond in position, appearance and intensity to those obtained with solutions B.

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R5 as the coating substance and the conditions described above under test A.1. Spray the plate with dilute potassium iodobismuthate solution TS2.

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

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

C. To a quantity of the oral solution containing 50 mg of Trimethoprim add 30 ml of sodium hydroxide (~ 4 g/l) TS and extract with two quantities of 50 ml of dichloromethane R. Wash the combined dichloromethane extracts with two quantities of 10 ml of sodium hydroxide (~ 4 g/l) TS and then with 10 ml of water R. Shake with 5 g of anhydrous sodium sulfate R, filter and evaporate to dryness. Carry out the test as described under 1.7 Spectrophotometry in the infrared region. The infrared spectrum of the residue is concordant with the reference spectrum of trimethoprim RS.

pH value (1.13). pH of the oral suspension, 5.0 – 6.5.

Related substances

Trimethoprim-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 80 volumes of chloroform R, 20 volumes of methanol R and 3 volumes of ammonia (260 g/l) TS as the mobile phase. Prepare a solvent mixture as follows: mix 8 volumes of chloroform R and 2 volumes of methanol R. Apply separately to the plate 5 µl of each of the following three solutions. For solution (A), transfer a volume of oral suspension, containing about 40 mg of Trimethoprim to a separation funnel. Extract with three portions of 25 ml of the solvent mixture; collecting the extracts in a 125 ml conical flask. Evaporate to dryness the combined extracts with the aid of a current of air on a steam bath. Dissolve the residue in 2 ml of the solvent mixture, then centrifuge. For solution (B) use 20 mg of trimethoprim RS per ml of the solvent mixture. For solution (C), dilute an accurately measured volume of solution B with the solvent mixture to obtain a solution having a known concentration of 0.1 mg per ml. After removing the plate from the chromatographic chamber, allow it to dry in air, and examine the chromatogram in ultraviolet light (254 nm).

Trimethoprim produces a spot at about RF 0.7 and the trimethoprim degradation product produces a spot at about RF 0.3 to 0.5. Any spot obtained with solution A at about RF 0.3 to 0.5 is not greater in size and intensity than the spot obtained with solution C (0.5%).
Sulfamethoxazole-related substances. Carry out the test as described under 1.14.1. Thin-layer chromatography, using silica gel R5 as the coating substance. Prepare an ethanol-methanol solution by mixing 95 volumes of dehydrated ethanol R and 5 volumes of methanol R. As the mobile phase, use a mixture of 25 volumes of the ethanol-methanol solution, 25 volumes of heptane R, 25 volumes of dichloromethane R and 7 volumes of glacial acetic acid R. Apply separately to the plate 50 µl of each of the following three solutions. For solution (A), transfer a volume of the oral suspension containing 200 mg of Sulfamethoxazole to a 100 ml volumetric flask containing 10 ml of ammonia (260 g/l) TS. Add 50 ml of methanol R, shake for 3 minutes, and dilute to volume with methanol R. Centrifuge a portion of the solution for 3 minutes. For solution (B), transfer 20 mg of sulfamethoxazole RS into a 10 ml volumetric flask, dissolve in 1 ml of ammonia (260 g/l) TS and dilute to volume with methanol. For solution (C), transfer 10 mg of sulfanilamide RS into a 50 ml volumetric flask, dissolve in 5 ml of ammonia (260 g/l) TS and dilute to volume with methanol R. Pipet 5 ml of this solution into a 100 ml volumetric flask, add 10 ml of ammonia (260 g/l) TS and dilute to volume with methanol R. For solution (D), transfer 10 mg of sulfanilic acid RS into a 50 ml volumetric flask, dissolve in 5 ml of ammonia (260 g/l) TS and dilute to volume with methanol R. Pipet 3 ml of this solution into a 100 ml volumetric flask, add 10 ml of ammonia (260 g/l) TS and dilute to volume with methanol R. For solution (E), transfer 3 mg of sulfamethoxazole N4-glucoside RS into a 50 ml volumetric flask, dissolve in 5 ml of ammonia (260 g/l) TS and dilute to volume with methanol R. For solution (F), transfer 10 mg of sulfanilamide RS, 6 mg of sulfanilic acid RS and 60 mg of sulfamethoxazole N4-glucoside RS into a 100 ml volumetric flask, dissolve in 10 ml of ammonia (260 g/l) TS and dilute to volume with methanol R. Pipet 1 ml of this solution into a 10 ml volumetric flask containing 20 mg of sulfamethoxazole RS, add 1 ml of ammonia (260 g/l) TS and dilute to volume with methanol R to volume.

After removing the plate from the developing chamber, allow it to dry in air, spray with 4-dimethylaminobenzaldehyde TS7 and allow the plate to stand for 15 minutes.

Any spots corresponding to sulfanilamide, sulfanilic acid and sulfamethoxazole N4-glucoside obtained with solution A are not greater in size and intensity than the spots obtained with solution C (0.5%), solution D (0.3%), and solution E (3.0%) respectively. The test is not valid unless the chromatogram obtained with solution F shows four clearly separated principal spots.

Assay

Either method A or methods B and C may be applied.

A. 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 base-deactivated silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm). Hypersil BDS C18 has been found suitable As the mobile phase, use a solution prepared as follows: mix 1400 ml of water R, 400 ml of acetonitrile R, and 2.0 ml of triethylamine R in a 2000 ml volumetric flask. Allow to equilibrate to room temperature, and adjust with acetic acid (~10 g/l) TS to pH 5.9. Dilute to volume with water R, and filter through a 0.45 µm membrane.

Prepare the following solutions. For solution (1) transfer an accurately weighed quantity of the oral suspension, containing about 80 mg of Sulfamethoxazole, to a 50 ml volumetric flask using about 30 ml of methanol R. Sonicate the mixture for
about 10 minutes with occasional shaking. Allow to cool to room temperature, make up to volume with methanol R, mix and filter. Transfer 5.0 ml of clear filtrate into a 50 ml volumetric flask, make up to volume with the mobile phase and mix. For solution (2), use 0.32 mg of trimethoprim RS and 1.60 mg of sulfamethoxazole RS per ml of methanol R. Transfer 5.0 ml of this solution into a 50 ml volumetric flask, make up to volume with the mobile phase.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm. Inject separately 20 µl of solutions (1) and (2) and record the chromatogram for 1.5 times the retention time of sulfamethoxazole. The test is not valid unless the resolution factor between the peaks due to sulfamethoxazole and to trimethoprim is at least 5.0.

Determine the weight per ml (1.3.1) of the oral suspension and calculate the percentage content of Sulfamethoxazole (C10H11N3O3S) and Trimethoprim (C14H18N4O3) in the oral suspension from the declared content of Sulfamethoxazole (C10H11N3O3S) and Trimethoprim (C14H18N4O3) in sulfamethoxazole RS and trimethoprim RS.

B. To 8.0 g of the oral suspension, accurately weighed, add 30 ml of sodium hydroxide (~ 4 g/l) TS, shake and extract with four quantities of 50 ml of dichloromethane R, washing each extract with the same two quantities of 10 ml of sodium hydroxide (~4 g/l) TS. Reserve the combined dichloromethane extracts for the Assay method C. Dilute the combined aqueous solution and washings to 250 ml with water R, filter and dilute 5 ml of the filtrate to 200 ml with water R (solution A). Carry out the following procedure protected from light using 2 ml of solution A. Add 0.5 ml of hydrochloric acid (~146 g/l) TS and 1 ml of sodium nitrite (~ 1 g/l) TS and allow to stand for 2 minutes. Add 1 ml of ammonium sulfamate (~ 5 g/l) TS and allow to stand for 3 minutes. Add 1 ml of N-(1-napthyl)ethylenediamine hydrochloride (1 g/l) TS and allow to stand for 10 minutes. Dilute the resulting solution to 25 ml with water R and measure the absorbance at 538 nm, using in the reference cell a solution prepared in the same manner but using 2 ml of water R in place of solution A. Dissolve 0.25 g of sulfamethoxazole RS in 50 ml of sodium hydroxide (~4 g/l) TS and dilute to 250 ml with water R. Dilute 5 ml of the resulting solution to 200 ml with water R (solution B). Repeat the procedure described above, using 2 ml of solution B and starting at the sentence “Add 0.5 ml of hydrochloric acid (~146 g/l) TS and 1 ml of sodium nitrite (~ 1 g/l) TS …”.

Calculate the content of Sulfamethoxazole (C10H11N3O3S) from the values of the absorbances obtained using the declared content of C10H11N3O3S in sulfamethoxazole RS. Determine the weight per ml (1.3.1) of the oral suspension, and calculate the content of Sulfamethoxazole (C10H11N3O3S), weight in volume.

C. Extract the dichloromethane solution reserved in the Assay for sulfamethoxazole with four quantities of 50 ml of acetic acid (60 g/l) TS. Wash the combined extracts with 5 ml of dichloromethane R and dilute the aqueous extracts to 250 ml with acetic acid (60 g/l) TS. To 10 ml of this solution add 10 ml of acetic acid (60 g/l) TS and sufficient water R to produce 100 ml. Measure the absorbance of the resulting solution at the maximum at 271 nm.

Calculate the content of Trimethoprim (C14H18N4O3) using 204 as value for the specific absorbance (ε) at the maximum at 271 nm. Calculate the content of Trimethoprim (C14H18N4O3), weight in volume.
New reagents to be added in Ph.Int.

**Acetic acid (~10 g/l) TS**
Acetic acid (~300 g/l) TS, diluted with water to contain about 10 g of C2H4O per litre.

**Hydrochloric acid (~146 g/l) TS**
Hydrochloric acid (~250 g/l) TS, dilute with water to contain approximately 146 g of HCl in 1000 ml (approximately 4 mol/l).

**Sodium hydroxide (~ 4 g/l) TS**
A solution of sodium hydroxide R containing about 4 g/l of NaOH (approximately 0.1 mol/l).

**4-Dimethylaminobenzaldehyde TS7**
Dissolve 0.1 g of 4-dimethylaminobenzaldehyde R in 1 ml of hydrochloric acid (~420 g/l) TS, dilute with ethanol (~750 g/l) to produce 100 ml.