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WHO Drug Information

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Reports on Individual Drugs

Women's Health Initiative Study

The Women's Health Initiative Study (WHI) was sponsored by the US National Institutes of Health to evaluate the effects of hormone replacement therapy (HRT). Results of the study have now been reviewed in many countries, and some highlights are proposed in the following summaries.

The study has several ongoing components, one of which was designed to assess the effects of conjugated equine estrogens and medroxyprogesterone acetate on the risk of developing heart disease. This arm was halted early in July 2002 when the independent data monitoring committee detected an excess risk in the estrogen/progestogen group: patients had a 26% increase in the relative risk of invasive breast cancer, a 41% increase in the risk of stroke and a 22% increase in heart disease compared to women taking placebo.

These results do not necessarily apply to lower doses of HRT or to other combination HRT products. Although there was an increase in vascular events, many of the women in the study had pre-existing risk factors for cardiovascular disease. However, since no long-term trials of combined hormone replacement therapy are continuing, the balance between benefit and harm will remain uncertain. It seems that hormone replacement therapy may continue to be prescribed for menopausal symptoms and osteoporosis prevention, but the need for continued use should be reviewed annually.

Menopausal combined hormone therapy update: Canada

The Women's Health Initiative (WHI) trial is a striking example of how scientific evidence can improve prescribing practice (1). Evidence on hormone replacement therapy in 1999 showed that long-term estrogen/progestin therapy to prevent cardiovascular disease for menopausal women with previous myocardial infarction would cause more harm than good (2). This conclusion was based on data from the Heart and Estrogen/Progestin Replacement Study (HERS) randomized controlled trial (RCT) (3). In July 2002, the follow-up of the HERS trial (HERS II) (4, 5) and the WHI (1) were published. These two trials strengthen the evidence against using combined hormone therapy to prevent cardiovascular disease.

WHI/HERS II details

WHI enrolled 16 608 healthy menopausal North American women with an intact uterus (mean age 63). The trial was stopped early (mean follow-up 5.2 years) because the independent data monitoring committee detected an excess of breast cancer in the estrogen/progestin group (1). HERS enrolled 2763 menopausal women with an intact uterus and history of coronary heart disease (mean age 67). In HERS II, 2321 women were followed in an open label extension (total mean follow-up 6.8 years) (4, 5).

The intervention in both trials was a daily tablet (0.625 mg of conjugated equine estrogens [CEE], plus 2.5 mg medroxyprogesterone acetate [MPA]); the control was an identical placebo tablet.

Both trials:

• Randomized large numbers of subjects, achieving, at baseline, an equal distribution of all known confounding factors in both groups (3, 6).

• Enrolled a population of women representative of those typically treated with hormone therapy in North America.

• Blinded both subjects and physicians to treatment allocation.

• Used independent data and safety monitoring boards.

• Used an independent committee to analyse, interpret, and publish the data.

However, a substantial number of women in both studies stopped taking the active study drug (42%
in WHI and 55% in year 6 in HERS II). This can lead to underestimation of treatment differences, but does not invalidate the differences demonstrated.

The results of HERS II and the WHI trial, published in July 2002, appear to have had an effect on women and physicians in the United States; US sales of the combination product used in the trials, Prempro®, dropped by 53% from May 2002 to September 2002. Over the same period sales of Premarin®, the CEE component fell by 22% (7).

### Conclusions

The implications for combined estrogen/progestin therapy are:

- Long-term combined hormone therapy leads to more harm than good in menopausal women whether they are healthy or have coronary artery disease. It is not a defensible preventive strategy (8).
- For severe vasomotor symptoms not controlled by other means, low dose estrogen (e.g., 0.3

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* calculated using Review Manager, Cochrane Collaboration. * p < 0.05.
+ Duration was 5-7 years in the 2 trials. RR = Relative Risk. CI = Confidence Interval.
ARR = Absolute Risk Reduction. NNT = Number Needed to Treat to prevent one event.
ARI = Absolute Risk Increase. NNH = Number Needed to treat to cause one Harmful event.
mg CEE for women without a uterus) or estrogen/progestin (e.g. 0.3 mg CEE/1.25 mg MPA for women with a uterus) can be prescribed for symptomatic benefit, as shown by the Women’s Hope randomized clinical trial (9).

- Symptomatic therapy should be limited to at most 1–2 years (11).
- Women prescribed combined hormone therapy should be alerted to the increased risk of venous thromboembolic disease, stroke and breast cancer, and reminded periodically if longer-term therapy is contemplated.

Implications for other menopausal hormone therapies:

- Until other hormone therapies (including estrogen alone or raloxifene) have been demonstrated to provide more good than harm in long-term randomized clinical trials, they cannot be recommended for preventive therapy without ignoring the lessons from these two landmark clinical trials (8).

References


Women’s Health Initiative data review: USA

The Food and Drug Administration (FDA) has advised of new safety changes to labelling of all estrogen and estrogen/progestin products for use by postmenopausal women. These changes reflect an analysis of data from the Women’s Health Initiative study (WHI), a study sponsored by the National Institutes of Health (1).

FDA will also be issuing updated guidance for manufacturers of estrogen and estrogen with progestin products regarding labelling of those products and development of new products for use in postmenopausal women. New labelling changes include a boxed warning and changes to the approved indications.

A component of the WHI study was designed to assess the effects of Prempro®, a combination of estrogens plus a progestin, on the risk of developing heart disease. The Prempro® arm of the WHI was halted early in July 2002 because the overall health risks, particularly the risks of invasive breast cancer and cardiovascular disease, exceeded the benefits of the drug. Estrogen and progestin hormones have never been approved by FDA for prevention of heart disease. FDA has requested that all other manufacturers of estrogen and estrogen with progestin drug products for use
in postmenopausal women make similar changes to the labelling for their products.

The new boxed warning highlights the increased risks for heart disease, heart attacks, strokes, and breast cancer. This warning also emphasizes that these products are not approved for heart disease prevention. FDA has also modified the approved indications for Premarin®, Prempro®, and Premphase® to clarify that these drugs should only be used when the benefits clearly outweigh risks. Of the three indications, two have been revised to include consideration of other therapies:

- Treatment of moderate to severe vasomotor symptoms (such as “hot flashes”) associated with the menopause. (This indication has not changed.)
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (dryness and irritation) associated with the menopause. When these products are being prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
- Prevention of postmenopausal osteoporosis. When these products are being prescribed solely for the prevention of postmenopausal osteoporosis, approved non-estrogen treatments should be carefully considered, and estrogens and combined estrogen-progestin products should only be considered for women with significant risk of osteoporosis that outweighs the risks of the drug.

The new labelling also advises health care providers to prescribe estrogen and combined estrogen with progestin drug products at the lowest dose and for the shortest duration for the individual woman. Women who choose to take estrogens or combined estrogen and progestin therapies should have yearly breast exams, perform monthly breast self-examinations, and receive periodic mammography examinations scheduled based on their age and risk factors. Women should also talk to their health care provider about other ways to reduce their risk factors for heart disease (e.g., high blood pressure, poor diet, tobacco use) and osteoporosis (e.g., an appropriate diet, use of Vitamin D and Calcium supplements, weight-bearing exercise).

FDA’s review of the WHI findings leads to some important research questions for the medical community. These questions include whether lower doses of estrogen and progestin will have lower risks, if other types of estrogens and progestins or other ways of administering these drugs, such as through patches, have different risks, and how best to stop taking estrogens and progestins.

References


2. FDA News, P03-018 January 2003

Future of hormone replacement therapy: Australia

The premature cessation of one arm of the ongoing US Women’s Health Initiative study (WHI) undoubtedly caused more media than scientific alarm (1). The study is very important, as it was one of only two studies of long-term hormone replacement therapy (HRT). Although the combined estrogen and progestogen arm was stopped, the dietary and estrogen-only arms continue. The combined HRT arm was stopped because the predetermined stopping point (a small but statistically significant increase in detected breast cancer) was reached. In addition, there was an increase in stroke and thromboembolism, and a trend to an increase in heart disease.

Although breast cancer increased by 8 cases per 10 000 women years there was no overall difference in cancer rates or mortality between the placebo and combined HRT groups. This was because HRT was associated with a reduction in bowel and uterine cancers. The results observed in the WHI study were of similar magnitude as those seen in the systematic reanalysis of observational studies (2) of women taking combined estrogen and progestogen. The early cessation of this arm of the study at 5.2 years prevents the assessment of later benefits and risks.

Cardiovascular disease

The reported results of WHI to date are little different from the published results of randomized trials looking at the secondary prevention of heart
disease. Most women enrolled in the WHI study were overweight, 80% were between 60 and 79 years of age, half had smoked and some had hypertension and increased concentrations of cholesterol. These cardiovascular risk factors suggest that many in the study could have had established atherosclerosis.

Recent studies suggest HRT may inhibit the process of atherosclerosis in healthy arteries soon after menopause (3) and observational studies in younger women starting HRT suggest a potential cardiovascular benefit (4). However, HRT may have a deleterious effect by destabilizing plaques in the atherosclerotic arteries of older women. Secondary prevention studies such as HERS (5) confirm an early increase in adverse cardiovascular events when HRT is first prescribed after a cardiac event.

To improve the power of the study for cardiac events the WHI enrolled many older women up to the age of 79 years. To what extent the effect of combined HRT seen in the WHI population applies to women commencing HRT at perimenopause remains debatable. The cardiovascular results of WHI are going to remain controversial until healthier and younger postmenopausal women are studied in a long-term trial.

Unresolved issues
A long-term randomized trial can study only a few therapeutic regimens. Only conjugated equine estrogens and medroxyprogesterone acetate were being tested in the long-term HRT trials, WHI and WISDOM (Women's International Study of long Duration Oestrogen after Menopause). No other HRT regimens are being tested. It is therefore impossible to know if HRT by non-oral routes, other estrogens, other progestogens or other drugs such as tibolone have different effects. It would be wise to counsel that the outcomes for other combined HRT products may be similar to those reported by the WHI.

To date, estrogen-only HRT does not have the same risk profile as combined estrogen and progestogen, and the estrogen-only arm of the WHI study continues. Most importantly the WHI study does not give the overall harm/benefit ratio for long-term HRT as many outcomes were not measured. These include quality of life, menopausal symptom control, cognitive function, dementia, urogenital health, arthritis, other cancers and the effects of HRT on other body parts, e.g. eyes, teeth, skin. All these outcomes and a better understanding of the effects of HRT on the cardiovascular system are still greatly needed. WISDOM (the UK, Australian and New Zealand 15-year trial of HRT) was looking at these outcomes, but the study has been discontinued (6). It is unlikely that we shall ever have good evidence to assess the risks, benefits and costs of long-term HRT.

It is important to emphasize that short-term trials of HRT show clear evidence of benefit for menopausal symptoms, especially vasomotor symptoms. These studies also show adverse effects which include start-up bleeding, breast tenderness and the uncommon but early risk of thromboembolism. The risk of breast cancer does not significantly increase until after five years of first use of combined HRT. The most pessimistic increase in breast cancer in all studies to date is one extra-detected breast cancer per 100 women after 10 years of use, but without an increase in breast cancer mortality. In women who have had a premature menopause and who require earlier HRT their risk at age 55 is approximately that of women commencing HRT at age 50. Long-term use in these women up to age 55 is appropriate.

Future prospects
It is not appropriate to prescribe HRT without an indication. The following points act as a guide to good practice.

• The main indication for HRT is control of menopausal symptoms and improvement of quality of life.

• Always counsel about the mixed risks and benefits of HRT and document this.

• Oral HRT is still the route of choice. Women with a uterus require combined HRT, through progestogen cyclically over perimenopause and continuously after menopause. Women with a uterus should not receive estrogen alone.

• In women who only have urogenital symptoms, local vaginal estrogens can be used.

• In women at risk of osteoprotic fractures, discuss and tailor therapies such as HRT, selective estrogen receptor modulators or bisphosphonates, together with lifestyle advice.

• HRT is not advocated for the treatment or prevention of cardiovascular disease.
• Women on HRT should be reviewed yearly to determine optimal therapy and time for cessation of treatment.

• After 4–5 years of therapy it is appropriate to offer a trial off HRT. The dose can be reduced over 1–2 months before cessation.

• In women who have a return of disabling symptoms, HRT can be re-introduced for further treatment periods at the lowest effective dose and at any time of their lives.

• Women who are aware of the currently known mixed benefits and risks of long-term therapy and who have found that they have a better quality of life on HRT can be prescribed long-term HRT.


References


6. Vikkers, M., Meade, T., Darbyshire, J. Hormone replacement therapy recommendations: New Zealand

At its meeting of 11 September 2002, the New Zealand Medicines Adverse Reactions Committee (MARC) reviewed studies examining the safety of hormone replacement therapy (HRT). On completion of its review, the MARC concluded that HRT provides a number of benefits with respect to control of symptoms associated with estrogen deficiency, such as flushing and night sweats, and in preventing loss of bone density. However, for most women, the risks associated with long-term use of HRT outweigh the benefits. These risks include:

• An immediate increase in the risk of venous thromboembolism (VTE) for all HRT products containing estrogen. The increase in relative risk seen for all forms of HRT is of a similar size to that seen for oral contraceptive pills. Given that the baseline risk of VTE increases with age, the absolute risk is larger than for oral contraceptives.

• An increase in the risk of stroke that becomes statistically significant beyond 2–3 years use of combined HRT.

• An increase in the risk of developing breast cancer that becomes evident following prolonged use (more than 4–5 years). While the increase in risk is small, it has been confirmed by several studies and applies to all forms of HRT. There is insufficient information available to determine how long the increased risk of breast cancer persists after cessation of HRT.

• A possible increase in the risk of coronary heart disease. The data clearly indicate that despite evidence of HRT lowering cholesterol levels in treated patients, use of combined HRT neither prevents nor inhibits the further progression of coronary heart disease. The MARC considered that the totality of research indicates that combined HRT may possibly increase the risk of developing coronary heart disease.

In the opinion of the MARC, the increased risk of breast cancer and stroke means that the benefit/risk ratio for combined HRT products becomes unacceptable for most women after about 3 to 4 years duration of use.
To improve the safe use of HRT, the MARC recommends that:

- HRT should normally be used only where menopausal symptoms are disruptive to the quality of life of the woman;

- HRT should not be used for the primary or secondary prevention of coronary heart disease or stroke;

- In most circumstances, the risks of long term treatment outweigh the benefits; and combined HRT generally should not be used for longer than 3-4 years;

- Estrogen-only HRT increases the risk of breast cancer and venous thromboembolism to a similar extent as combined HRT;

- All prospective and current users of HRT should be advised of the risks and benefits of estrogen and progestogens;

- The need for continued treatment with HRT should be reviewed at the woman's next visit to her general practitioner and thereafter on a yearly basis.

http://www.medsafe.gov.nz
Vaccines and Biomedicines

Quality assurance and safety of biologicals

In order to assure the quality and safety of biological medicines and in vitro diagnostic procedures, the WHO Expert Committee on Biological Standardization provides guidance and technical specifications through the establishment of international reference preparations and recommendations for the production and control of biological products. The following summary sets out the decisions made by the Expert Committee at its recent meeting in Geneva*. A detailed report will be published in the WHO Technical Report Series. Information is also available on http://www.who.int/biologicals.

Production and quality control recommendations

Four documents were established on the production and quality control of biological medicines.

Elimination, reduction or replacement of thiomersal from licensed vaccines

Making changes to the thiomersal content of vaccines already licensed with this preservative is a complex issue that requires careful consideration. Experience has shown that eliminating or reducing thiomersal from an existing product may have an unexpected effect on vaccine quality, safety, efficacy or stability. The amount of additional data required to demonstrate that a product with an altered thiomersal content is at least of the same quality as the previous one containing thiomersal will need to be evaluated on a case by case basis. Such a decision should be science-based with a clear rationale for any change in the formulation, while taking into account the different implications of reducing or eliminating thiomersal from the production steps and/or from the final stage of production. Any change in the formulation may have an important impact on the quality, safety and efficacy of the vaccine and, as a consequence, these products may need to be considered as new vaccines requiring further clinical trial. The policy of whether to use thiomersal is discussed in the Vaccines and Biologicals: Recommendations from the Strategic Advisory Group of Experts (1).

Production and quality control of smallpox vaccines

Recommendations for production and quality control of smallpox vaccines were last revised in 1965. Since that time, intensified global eradication took place from 1967 to 1980 and the last naturally occurring case of smallpox was documented in 1977.

The Global Commission that certified eradication concluded that the likelihood of reintroduction of smallpox was negligible. Nevertheless, it recommended that WHO and national health authorities should be prepared for unforeseen events. Accordingly, stockpiles of vaccine were established and seed lots of vaccine were maintained in designated WHO Collaborating Centres. A survey conducted by WHO in 2001 found that only small amounts of stockpiled smallpox vaccines still exist. These stocks are unevenly distributed throughout the world and accessible only to a small segment of the global population. Additional production would be needed to meet any major demand on vaccine supply such as might follow an intentional release of smallpox vaccine.

Global resumption of smallpox vaccine production would benefit from modern concepts of production and control and current regulatory requirements

for licensing. Revised recommendations incorporate these principles and provide state of the art guidance for new vaccine manufacture and testing for substrates.

**Guidelines for the safe production of inactivated poliovirus vaccines**

*The WHO Recommendations for Production and Quality Control of Poliomyelitis Vaccine (Inactivated)* were last revised in 2000. At that time, it was clear that production and quality control of inactivated poliomyelitis vaccine (IPV) manufactured from wild poliovirus strains should comply with laboratory biosafety conditions in the context of a polio-free world and the need for effective containment of wild poliovirus strains as a precondition of global certification of eradication.

The new guidelines specify steps needed to minimize the risk of reintroducing wild poliovirus from a vaccine manufacturing facility into the community. Where infectious materials come into contact with permissive cells or animals, high containment (Biosafety Level 3/polio) measures are required. Biosafety Level-3/polio requires the primary and secondary containment of wild poliovirus infectious materials, with provisions governing air, water and materials entering and leaving the facility, specific requirements for personal protective clothing, laboratory design, the use of laboratory equipment, and medical surveillance of laboratory staff.

Additionally, it requires vaccination of all staff, appropriate biosafety training, and validation and documentation of physical and operational requirements. Implementation of containment conditions within IPV production and quality control testing facilities must also take into account the large quantities and concentrations of live vaccine that are produced, industrial scale of facilities, and existing rules and regulations governing the manufacture and testing of medicinal products, commonly known as good manufacturing practices (GMP).

Both biosafety and GMP share contamination control as a major concern. Where GMP prioritizes the safety of the patient being treated with the medicinal product, biosafety is primarily concerned with the protection of personnel and the surrounding environment. These concepts are not mutually exclusive, and a considerable area of overlap exists between the two. Where it may not always be possible for facilities and procedures to meet the ideal situation from both GMP and biosafety perspectives, some degree of flexibility has been introduced in the guidelines to satisfy both objectives. A number of the internationally harmonized GMP guidelines — such as those of WHO or the European Union — have introduced specialized GMP requirements for biological products.

**Guidance on the use of serological surrogates of protection for meningococcal C conjugate vaccines**

At its previous meeting, the Expert Committee adopted *Recommendations for the production and control of group C meningococcal conjugate vaccines*. The Committee agreed to draft an addendum on serological assays to evaluate the immune responses to these vaccines and to review the current recommendations in the light of data emerging from the United Kingdom following the introduction of the vaccine and, in particular, data related to the demonstration of immunological memory.

An addendum has now been prepared stating that different lots of single component or combined meningococcal C conjugate vaccine from each manufacturer should be evaluated for immunogenicity, including the induction of immunological memory, in the target age group before licensing. Two assays are utilized to measure immunogenicity in these vaccines, the serum bactericidal antibody assay (regarded as the “gold standard”) and serogroup C-specific IgG ELISA.

National regulatory authorities should ensure that data made available to them are relevant to national immunization programmes so that appropriate schedules may be developed regarding vaccine co-administration. For combinations of group C meningococcal conjugate vaccine and other antigens, either pre-combined or to be given by mixing immediately before injection, the national regulatory authority should ensure that there are adequate studies to demonstrate that there is no clinically significant interference with the immunogenicity or induction of immunological memory by the meningococcal C conjugate component.

**Transmissible spongiform encephalopathies**

A WHO Consultation on transmissible spongiform encephalopathies in biological and pharmaceutical products was held in Geneva in February 2003. The meeting considered the risks of transmission both from animal to humans, and between humans. It was agreed that bovine spongiform encephalopathy (BSE) presents a global risk to the food chain. Cases of variant CJD (vCJD) have occurred in a number of countries and there have been changes over time in the
epidemiology of BSE and vCJD. It was agreed that the conclusions and recommendations of this consultation would supersede WHO guidance published in 1997.

**Recommendations for biological reference materials**

*Guidelines for preparation, characterization, and establishment of International and other standards and reference reagents for biological substances* were published in 1990 (2). A revision has now been drafted in which a substantial number of changes are proposed including the addition of a new section on quality assurance, and the concept of regional reference materials.

The Committee noted the revision and recommended the addition of an expanded section addressing the scientific basis for calibration and potency assignment, and how to design such studies and their statistical analysis. Additional guidance on the role and use of WHO reference materials was considered important.

**Vaccines**

**Diphtheria and tetanus vaccines**

A WHO Consultation on the potency, assay and measurement of consistency of diphtheria and tetanus vaccines was held at Bilthoven, Netherlands in December 2002. Although these vaccines have been used successfully over a long period of time in many countries, the absence of an international agreement on assay procedures and minimum potency requirements is adversely affecting the development of combination vaccines and international distribution.

The meeting reviewed progress towards simplified lot release assay and resolution of technical issues. It was agreed that the control vaccine for assays should not be a clinical lot but a heterologous, generic preparation. Clear guidance will be needed on the circumstances under which the simplified assay may be used. Such developments will require revision of the present Requirements (3).

**Preclinical evaluation of vaccines: regulatory expectations**

A guideline has been drafted on preclinical evaluation of vaccines to provide guidance to regulatory authorities and manufacturers. This is proposed as a companion document to the *Guidelines on Clinical Evaluation of Vaccines* adopted by the Expert Committee at its Fifty-second meeting in 2001 (4) and as reviewed at a WHO Informal Consultation held in Geneva in December 2002. The Committee recommended that the scope of the document be focused on preventive and therapeutic vaccines for infectious diseases at this stage, although the scope could be expanded in the future. It also made a number of suggestions to the drafting group.

**Oral poliovirus vaccine**

A meeting on quality control of monovalent bulks of oral poliovirus vaccine (OPV) held in November 2002 reviewed 20 years' experience of applying the WHO neurovirulence test for polio to more than 1000 batches. Although some deviations from the recommended procedure had occurred, the results remained valid.

Because expertise in this test procedure is scarce, it was recommended that WHO ensure maintenance of competence and good practice in neurovirulence testing in at least two laboratories. The existing histopathological slides are a unique resource and they should be archived for later use, particularly for training purposes.

Finally, it was recommended that remaining stocks of WHO OPV reference materials should be centralized at the WHO International Laboratory for Biological Standards, United Kingdom, in order to facilitate their availability.

**Blood products**

The goal of the *Requirements for the Collection, processing and quality control of blood, blood components and plasma derivatives* is to ensure the safety of blood and blood products, to assure suitable quality of plasma for fractionation, and to provide the principles on which formulation of local requirements by regulatory authorities can be based. The requirements were last revised in 1992 (5) and the Expert Committee concluded that a complete revision would be needed.

Guidance on good manufacturing practice is also needed and should be integrated into the requirements. The Expert Committee welcomed a proposal to begin revision and requested the Secretariat to consult with appropriate bodies, such as national regulatory authorities and the Global Collaboration on Blood Safety, and to report back to the next meeting.

**International Reference Materials**

The scientific basis for preparation and characterization of WHO International Standards and Reference Materials was discussed at the
New or replacement international standards or reference reagents established by the Fifty-third WHO Expert Committee on Biological Standardization

**ADDITIONS**

### Antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Concentration</th>
<th>Type</th>
</tr>
</thead>
</table>

### Blood products and related substances

<table>
<thead>
<tr>
<th>Substance</th>
<th>Concentration</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A RNA</td>
<td>50 000 IU/vial</td>
<td>First International Standard 2003</td>
</tr>
<tr>
<td>Hepatitis C RNA</td>
<td>50 000 IU/vial</td>
<td>Second International Standard 2003</td>
</tr>
<tr>
<td>HIV-1 RNA genotypes</td>
<td>No assignment</td>
<td>First International Reference Panel 2003</td>
</tr>
</tbody>
</table>

### Cytokines, growth factors and endocrinological substances

<table>
<thead>
<tr>
<th>Substance</th>
<th>Concentration</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoietin, recombinant</td>
<td>120 IU/ampoule</td>
<td>Second International Standard 2003</td>
</tr>
</tbody>
</table>

### MISCELLANEOUS

<table>
<thead>
<tr>
<th>Substance</th>
<th>Concentration</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human brain, CJD control</td>
<td>No assignment</td>
<td>First Reference Reagent 2003</td>
</tr>
<tr>
<td>Human brain, sporadic CJD preparation 1</td>
<td>No assignment</td>
<td>First Reference Reagent 2003</td>
</tr>
<tr>
<td>Human brain, sporadic CJD preparation 2</td>
<td>No assignment</td>
<td>First Reference Reagent 2003</td>
</tr>
<tr>
<td>Human brain, variant CJD</td>
<td>No assignment</td>
<td>First Reference Reagent 2003</td>
</tr>
</tbody>
</table>

(These 4 preparations are supplied together as the Human CJD Reference Panel. Also available separately)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Concentration</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polio virus type 2 for MAPREC assay</td>
<td>0.67% 481-G</td>
<td>First International Standard 2003</td>
</tr>
<tr>
<td>MAPREC assay of polio virus type 2 (high mutant virus)</td>
<td>1.21% 481-G</td>
<td>First International Reference Reagent 2003</td>
</tr>
</tbody>
</table>

The availability of these reference preparations is indicated in the WHO Catalogue at http://www.who.int/biologicals
Meeting. One view is that standardization should be based on a reference system using a hierarchy of metrological determinations that provides traceability of measurement and an indication of the level of uncertainty attached to measurements. This approach differs from that historically used by WHO for assigning unitage to the biological activity of biological reference materials. This is because biological activity is not an SI unit and although the International Unit is assigned arbitrarily, the continuity of the International Unit with replacement reference materials is ensured by inclusion of the previous materials in the collaborative studies.

Where multimolecular biological species are being studied, multiple methods provide valuable scientific information about specificity. However, the approach of using a single reference method to generate a value in SI units with an associated uncertainty is not usually appropriate. In addition, the Committee noted that scientific developments may mean that reliance on a single method is not appropriate. Methods developed later may well be more specific, accurate and precise and some methods, such as those dependent on extensive use of animals, are no longer acceptable.

In some cases, improved specificity has resulted in the establishment of WHO reference materials with a defined, restricted use, e.g. for bioassay or immunoassay. Further, scientific advances have resulted in discontinuation of many biological reference materials because the substances are capable of characterization solely by physical and chemical methods. The Committee confirmed that full evaluation of an analyte by biological, physical, chemical and medical properties should guide their decision on the basis of assignment of activity.

A further consideration is that the WHO reference materials are primary standards for calibration of therapeutic products and the ISO Guide 35 on Reference Materials explicitly indicates that reference materials for pharmaceutical use do not have an uncertainty stated with their assignment of content.

The Committee recommended that issues relating to the scientific basis for characterization and value assignment to biological reference materials should be addressed in the revision of the guidelines for establishment of such materials.

References

Direct-to-consumer drug advertising: survey results

The US Food and Drug Administration (FDA) has released results of its survey on direct-to-consumer (DTC) advertising for prescription drugs among 500 physicians. The results show that DTC advertising, when carried out correctly, can serve positive public health functions such as increasing patient awareness of diseases that can be treated, and prompting thoughtful discussions with physicians that result in needed treatments being prescribed — often not the treatment in the DTC advertisement. This study also demonstrates that most physicians view DTC advertisements as one of many factors that affect their practice and their interactions with patients, both positively and negatively.

Highlights include:

• Many physicians believe that DTC can play a positive role in their interactions with patients. For example, most agreed that, because their patients saw a DTC ad, he or she asked more thoughtful questions during the visit. Some thought that the ad made their patients more aware of possible treatments.

• Many physicians also thought that DTC ads made their patients more involved in their health care.

• Physicians also felt they had to provide additional information to patients beyond what patients retained from the DTC advertising. About 75% of physicians believed that DTC causes patients to think the drug works better than it did, and many physicians felt some pressure to prescribe something when patients mentioned DTC ads.

• However, 8% felt very pressured to prescribe the specific brand name drug when asked about it. Instead, physicians suggested alternative courses of action for a variety of reasons: a different drug was more appropriate, there were side effects the patient did not know about, or a less expensive drug was available.

• According to the survey, one effect of DTC ads was to help educate patients about their health problems, and to provide greater awareness of treatments. The study demonstrated that when a patient asked about a drug, 88% of the time they had the condition that the drug treated. And 80% of physicians believed patients understood what condition the drug treats.

• Moreover, doctors believe that patients understand they need to consult a health care professional about appropriate treatment: 82% of physicians believe patients understand very well or somewhat that only a doctor can decide if the drug is right for the patient. This is important, because only 40% of physicians believe that patients understood very well or somewhat well the possible risks and negative effects of an advertised drug from the DTC ad alone.

This is the third survey conducted by FDA to help the agency assess the impact of DTC advertising. FDA will continue to analyse these data, and will continue its comprehensive evaluation of DTC advertising and its impact on public health, to ensure that current DTC policies maximize the positive benefit that DTC advertising can play in the public health arena.


Race and ethnicity data in clinical trials

The United States Food and Drug Administration (FDA) has published a draft Guidance for Industry to recommend categories for collecting effectiveness and safety data during clinical trials for ethnic and racial demographic groups.

FDA regulations require drug sponsors to present an analysis of data according to age, gender and race. An analysis of modifications of dose or dosage intervals for specific groups is also required when manufacturers submit a new drug application for approval by FDA. To accomplish this, drug manufacturers are recommended to use
the race and ethnicity categories during clinical trial data collection to ensure consistency in evaluating potential differences in drug response among racial and ethnic groups.

Some differences in response to medical products have already been observed in distinct groups of the US population. These differences may be attributable to intrinsic factors such as genetic differences; to extrinsic factors like diet, environmental exposure, sociocultural issues, or to interactions between these factors. For example, in the United States, whites are more likely than people of African or Asian heritage to have low levels of an important enzyme (CYP2D6) that metabolizes antidepressants, antipsychotics, and beta blockers.

Additionally, of some drugs in the psychotherapeutic class, slower enzyme metabolism has been observed in persons in the United States of Asian descent as compared to Whites and Blacks. Other studies have shown that Blacks respond less to several classes of antihypertensive agents (beta blockers and angiotensin converting enzyme (ACE) inhibitors). Racial differences in skin structure and physiology have been noted that can affect response to dermatological and topically applied products. Clinical trials have demonstrated lower responses to interferon-alpha used in the treatment of hepatitis C among Blacks when compared to other racial groups.

The draft guidance does not discuss increasing the number of studies in which certain groups are exposed to a product, nor does it discuss increasing the total number of participants involved in clinical trials.


HIV vaccine update

Preliminary results of a large-scale trial of a candidate AIDS vaccine (AIDSVAX®) have been announced by the biotechnology company VaxGen. The trial was a three year, multinational randomized, double-blind placebo controlled Phase III trial of AIDSVAX (rgp120) to prevent HIV infection. The study did not show a significant reduction of HIV infection as a whole. For the majority of the participants — who were Caucasians — the effect of the vaccine was minimal. The company stressed that the results announced represent findings from an initial analysis and that additional studies will be conducted over the coming weeks to further clarify the data.

The AIDSVAX Phase III trial was the first large-scale human trial of an HIV vaccine. The trial was made possible through the involvement of over 5400 volunteers from the United States, Canada, and the Netherlands, the majority of whom were men who have sex with men. The vaccine used in this trial was designed to reduce susceptibility to infection with HIV subtype B, which is prevalent in the Americas, Western Europe, Australia, and New Zealand. To date, eleven subtypes of HIV-1 have been identified. Thus, one of the major challenges in HIV vaccine development is to develop one or multiple vaccines effective against all major subtypes of HIV.

VaxGen is also conducting another Phase III trial in Thailand, involving a vaccine candidate based on HIV subtypes B and E. That trial, which involves more than 2500 volunteers (mostly injecting drug users) is expected to provide additional information about the potential efficacy of this type of candidate vaccine. Results are expected by late 2003. VaxGen is also currently conducting pre-clinical research to develop a vaccine against the most common subtype, subtype C, which accounts for approximately 50% of all new HIV infections worldwide.

Several other candidate vaccines based on different HIV subtypes are being tested by other public and private organizations, mostly in the United States and Europe, but also increasingly in developing countries, where a total of 22 vaccine candidates have been or are being tested including in Brazil, Haiti, Kenya, Peru, Thailand, Trinidad and Tobago, and Uganda. At least one of these candidate vaccines is expected to enter Phase III trials this year in Thailand, with results available four years later.

References


Drug bar code regulation proposed

In an effort to improve patient safety in the hospital setting by reducing medication errors, the Food and Drug Administration (FDA) has published a proposed rule entitled Bar Code Label Requirements for Human Drug Products and Blood. Medical errors have substantial costs in lives, injuries, and wasted health care resources, and misuse of drugs is a major component of those errors.

Bar codes would be required on prescription drugs, over-the-counter drugs packaged for hospital use, and vaccines. The bar code would, as a minimum, contain the National Drug Code number, which uniquely identifies the drug, its strength, and its dosage form. The FDA is seeking comment on whether to add information such as lot number and expiry date. The proposed rule would also cover blood and blood components.

Once implemented, the bar code rule is estimated to result in a 50% increase in the interception of medication errors at the dispensing and administration stages resulting in 413,000 fewer adverse events over the next 20 years. Bar codes may also help prevent other types of medication errors in prescribing and transcribing because they will encourage health care organizations to adopt computerized systems for handling prescriptions. In the retail setting, pharmacists may use the bar codes in conjunction with computerized prescription orders to confirm that the right drug is being dispensed to the right patient. Pharmacies will benefit from standard codes that will be used by all prescription manufacturers.

Drug manufacturers will benefit from uniform standards. Installation of scanning systems may lead to improved purchasing and supply utilization and other potential risk management activities.

Reference: FDA Talk Paper, 13 March 2003

Terminology in pharmacogenetics

As a result of the development within the areas of genetics and genomics, changes are likely to occur in the way drug development is currently being conducted and the way medicines will be used. The use of terms that are harmonized and widely accepted by the stakeholders would contribute to better understanding and information exchange, particularly among investigators, ethics committees and subjects (participants).

Following extensive consultation, the European Agency for the Evaluation of Medicinal products (EMEA) has published a position paper on terminology in pharmacogenetics. This focuses on a specific set of critical terms that are frequently used in protocols for pharmacogenetic testing and that are relevant to define appropriate levels of protection for the privacy of subjects when describing how the results and samples will be used in clinical trials. At the present time, the definitions for pharmacogenetics and pharmacogenomics have not been agreed. For the sake of the position paper:

• Pharmacogenetics is the study of interindividual variations in DNA sequence related to drug response; and
• Pharmacogenomics is the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery and clinical development.

It is recognized that DNA data unique to a subject could potentially be used to reconstruct a link between a subject’s medical record and genotype information. Therefore, the most appropriate term level for a particular study depends on the nature of the research, intended use of the data, regulatory and legal environment and specific concerns of the investigator and study sponsor. The choice must respect the needs for the privacy of subjects participating in a clinical trial.

The processes by which samples and data are collected, labelled and stored have a direct effect on how the samples and results obtained can be used in the future and on the obligations of the investigator and sponsor to the sample subject. This pertains particularly to situations when a subject withdraws consent and affects the possibility of returning information, of withdrawing a sample for future analyses and verification of data ascribed to a subject in reports and regulatory submissions.

Five definitions for the labelling and coding of pharmacogenetic samples and data are proposed describing direct implications for handling of samples for pharmacogenetic testing and corresponding consequences for the level of privacy.
### Summary of five sample labelling terms

<table>
<thead>
<tr>
<th>Sample labelling category</th>
<th>Link between subject identity and pharmacogenetic data</th>
<th>Records identifiable for clinical monitoring</th>
<th>Actions possible if subject withdraws consent</th>
<th>Return of individual results to subject</th>
<th>Scope of subject privacy protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identified</td>
<td>Yes, directly</td>
<td>Yes</td>
<td>Sample can be withdrawn with immediate effect for any prospective use</td>
<td>Possible</td>
<td>Similar to general healthcare confidentiality</td>
</tr>
<tr>
<td>Single coded</td>
<td>Indirectly, via code key</td>
<td>Yes, via protocol-specified procedures</td>
<td>Sample can be withdrawn with immediate effect for any prospective use</td>
<td>Possible</td>
<td>Standard for clinical research Conforms to principles of GCP</td>
</tr>
<tr>
<td>Double-coded</td>
<td>Very indirectly, via two sets of code keys</td>
<td>Yes, via protocol-specified procedures</td>
<td>Sample can be withdrawn with immediate effect for any prospective use</td>
<td>Possible</td>
<td>Double code offers added privacy protection over single code</td>
</tr>
<tr>
<td>Anonymized</td>
<td>No, Key(s) identifying link between pharmacogenetic data and identity of subject deleted</td>
<td>No</td>
<td>Sample and data are not identifiable. Sample cannot be withdrawn once key is deleted</td>
<td>Not possible</td>
<td>Pharmacogenetic data not linked to individuals</td>
</tr>
<tr>
<td>Anonymous</td>
<td>No</td>
<td>No</td>
<td>None</td>
<td>Not possible</td>
<td>Complete</td>
</tr>
</tbody>
</table>

Protection and use of information for regulatory purposes. Duration of retention of the sample or its destruction needs to be defined in the protocol and in the consent form.

New tool to boost access to quality medicines and detect counterfeits

To improve the quality and efficacy of medicines, facilitate control of counterfeit and substandard drugs and address problems of drug resistance, the World Health organization has released a new edition of The International Pharmacopoeia (see page 39).

The International Pharmacopoeia provides specifications for the content, purity and quality of active ingredients and pharmaceutical products according to internationally approved standards. While a practical tool for all settings, it is aimed especially at those countries where national regulatory authorities may not have enough funds or staff to function effectively.

The International Pharmacopoeia will be particularly useful in identifying counterfeit and substandard medicines. These are growing concerns worldwide and especially affect developing countries. A recent survey found that 40% of artemisinin-based antimalarials were counterfeit they contained no active ingredients. Although countries do not always reveal data about the substandard quality of medicines, those that do demonstrate that on average 10–20% of medicines in developing country markets are substandard.

Concerned especially with increasing access to effective treatment, The International Pharmaco-
poeia gives priority to medicines for illnesses affecting developing country populations disproportionately, such as HIV, tuberculosis, malaria and diseases neglected by conventional pharmaceutical markets. In its Fifth Volume, The International Pharmacopoeia includes all artemisinin-based antimalarials known to date. These are now seen as the most effective medicines to treat drug-resistant malaria, affecting about 40% of the 500 million people contracting malaria yearly.

The monographs contained in the The International Pharmacopoeia can be used in any country or setting. For this purpose, they are designed to cater for both high-technology methods of testing or, when these are not available, for alternative methods which are less technically demanding.

In addition to monographs, WHO publishes basic tests for confirmation of the identity of active ingredients. These are especially useful when a fully equipped laboratory and analytical expertise are not available and when rapid control is needed. Publication of The International Pharmacopoeia is part of a comprehensive WHO programme to help regulatory authorities, health services and manufacturers assure the quality of medicines and to eliminate substandard products. Other elements of the programme include active support to regulatory authorities on combating counterfeit medicines, training in good manufacturing practices, and quality assessment of manufacturers of medicines.

Safety Issues

WHO Drug Dictionary: new structure – new focus

For those working in pharmacology and drug safety, the WHO Drug Dictionary (WHO-DD) has been an international consolidated reference source of drug names and related information for over 20 years. During that time, the Drug Dictionary has evolved to meet the needs of users, including national pharmacovigilance centres, pharmaceutical manufacturers, pharmacists and drug regulatory authorities. The WHO-DD has now been updated to provide a more user-friendly enhanced format.

The WHO-DD is a vital tool for coding drug safety information, both pre- and post-approval. A vast majority of pharmaceutical companies, international clinical research organisations, national drug monitoring centres and regulatory authorities continue to use the tool on a daily basis.

Update process

The WHO Drug Dictionary (WHO-DD) contains a listing of those drugs previously recorded in adverse reaction reports, whether suspected of having caused the reaction or not. WHO-DD also includes drugs from clinical trials. Data is obtained from the WHO Adverse Reactions Database, official drug regulatory or other dependable sources, national drug compendia, and notifications from the pharmaceutical industry.

The new WHO Drug Dictionary is not only a new file structure or a new focus – it also allows for additional types of product entries. For example, it is becoming increasingly apparent that all concomitant medication should be recorded and analysed in clinical studies and spontaneous adverse reaction reports.

WHO-DD entries are increasingly prompted by companies and regulators, either when products are launched on the market or found missing in the dictionary. The user simply sends the drug name or substance they would like to have entered together with available information sources, and it will be entered into the database. This service is carried out by the WHO Collaborating Centre for International Drug Monitoring with exactly the same quality assurance procedures to validate data sources as with regular updating. When new data is to be included in the next quarterly update the service is free of charge, while expedited updating can be carried out within three working days on payment of a fee.

The new WHO-DD has retained the functionality of the old system while adding a number of new features. The database now allows for coding of much more detailed information and contains more entries. Each entry in the new dictionary represents one marketed product, with accompanying information on trade name, dosage form, strength, as well as the country in which it is marketed and the company responsible (market authorization holder) for the product in the country. This means that one entry in the old dictionary will now become several entries in the new.

Extracts of the whole database or new additions and changes are available on a quarterly basis. Different formats are also provided as independent files. An internet-based search tool will soon replace the client server search programme.

WHO Drug Dictionary key points

- International standard for over 20 years
- Consistent, quality assured, prompt information entry.
- A hierarchical structure that allows easy and flexible data retrieval and analysis at different levels of precision.
- Chemical and therapeutic groupings using WHO drug record number system and ATC classification.
- Regular, responsive updating of structure and content.
- Computerized, software-independent format, for easy implementation in user systems.
Classification

Anatomical Therapeutic Chemical (ATC) classification is an integral part of the WHO-DD. The ATC classification is a hierarchical classification used to facilitate browsing in the dictionary and, more importantly, aggregation of statistical data for improved analysis. All drugs in the WHO-DD are assigned group/level codes according to the ATC classification. Products are coded with ATC codes approved for their generic group or name (International Nonproprietary Name). In addition, it is possible to code each product with the ATC code of most common use. This allows analysis and comparison of the drugs using the ATC classification.

Herbal medicines

In recent years, the WHO Collaborating Centre for International Drug Monitoring has made significant progress in classification of herbal substances. The WHO-DD already contains information on commonly used herbal medicines, but the coverage of traditional medicines and herbal substances is expanding considerably both in terms of quantity and quality. In collaboration with other organizations, a large number of trade names of herbal products will soon be available in the Dictionary, together with classifications of ingredients and a new ATC (Anatomic Therapeutic Chemical) classification customized to fit specific herbal classes. This new ATC classification is built on and compatible with the classification currently used for pharmaceuticals.

Transition and growth

The latest update of the WHO Drug Dictionary retains all previous fields which are mapped to the new structure. In particular, the current drug record number system is retained in the new database structure. There is a transition period while the previous version of WHO-DD is fully superseded by this more detailed version ending February 2003. A computerized tabulation which allows users to trace all changes that have been made in the Drug Dictionary since 1992 is also available.

New features and information (December 2002)

- New data fields.
- Product type (medicinal/herbal, etc).
- Dosage form and strength.
- Market authorization holder (company responsible for marketing).
- Country.
- Data of last change.
- Full integration with Anatomical Therapeutic Chemical classification.

The Drug Dictionary grows at a rate of more than 2200 entries each year. An on-line tutorial/course is provided by the WHO Collaborating Centre for International Drug Monitoring.

WHO Collaborating Centre for International Drug Monitoring

Providing an essential tool such as the WHO-DD to a diverse a group of users is a challenge which clearly requires two-way communication. The WHO Collaborating Centre for International Drug Monitoring provides formal channels for feedback: user group meetings take place in Europe and the USA each year, during international conferences, and an on-line discussion group has recently been set up. The Centre is always interested to hear users’ comments for improvements.

The year 2003 will be eventful for the WHO Drug Dictionary. A large number of new entries will be added, both medicinal and herbal products. More detailed information is available from the WHO Collaborating Centre for International Drug Monitoring http://www.who-umc.org e-mail: marie.lindquist@who-umc.org

The objectives of the WHO Collaborating Centre for International Drug Monitoring are to work with WHO to:

- Coordinate the WHO Programme for International Drug Monitoring and its national centres.
- Collect, assess and communicate information from national centres about the benefits, harm, effectiveness and risks of drugs.
- Alert the regulatory authorities of WHO Member States about potential drug safety problems.
- Promote the development and practice of pharmacovigilance in WHO Member States.

The main focus and source of data in pharmacovigilance are reports of adverse drug reactions (ADRs) from national centres in the Programme.
Tramadol – safety experience

Tramadol (Tramål®) is a centrally acting analgesic which has been available in Australia for four years. Although chemically unrelated to the opiates, it stimulates opioid receptors and inhibits noradrenaline and serotonin uptake.

The Australian Adverse Drug Reactions Committee (ADRAC) has received 354 reports associated with tramadol. The most common reactions include nausea, vomiting, sweating, dizziness, rash, tremor and headache. The more serious adverse reactions reported are:

<table>
<thead>
<tr>
<th>Reaction</th>
<th>No. of reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>36</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>30</td>
</tr>
<tr>
<td>Convulsions</td>
<td>26</td>
</tr>
<tr>
<td>Serotonin syndrome</td>
<td>20</td>
</tr>
<tr>
<td>Increase in blood pressure</td>
<td>14</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>12</td>
</tr>
<tr>
<td>Hepatic reactions</td>
<td>10</td>
</tr>
<tr>
<td>Warfarin interaction</td>
<td>5</td>
</tr>
</tbody>
</table>

For the cases of convulsions, the median time to onset was 2 (range 1–19) days. Tramadol was the only suspected drug in 11 cases, but in 14 other cases the patient was taking additional drugs which may lower the seizure threshold, including propofol, bupropion, hydrocortisone, morphine, and tricyclic antidepressants. One patient had a history of epilepsy, and was also taking carbamazepine and phenytoin.

Tramadol may cause serotonin syndrome, particularly when it is used at high doses or in combination with other agents increasing serotonin levels (1). In 16 of the 20 cases, the patient was taking potentially interacting medicines including moclobemide, SSRIs, tricyclic antidepressants, sibutramine and St John’s wort. Increases in hepatic enzymes were reported in 10 cases. One patient developed hepatic failure and died. All times to onset were short (range 1–19 days; median 9 days).

Tramadol may interact with warfarin to decrease prothrombin activity, although the mechanism is unknown (2). ADRAC has received five reports of this interaction. Monitoring should be considered when tramadol is started in patients taking warfarin. Although tramadol acts on opioid receptors, dependence and abuse appear to be rare (3). ADRAC has, however, received 11 reports of withdrawal symptoms with tramadol.

The use of tramadol has increased rapidly, with dispensings of oral formulations rising from 23 000 in 2000 to 580 000 in 2001 and over 1 100 000 in 2002. Prescribers should be alert to the more serious adverse reactions, especially those of a neuropsychiatric nature (4).

References


Minocycline and intracranial hypertension

Benign intracranial hypertension, also known as pseudotumour cerebri, involves a persistent rise in cerebrospinal fluid pressure. It is characterized by headache, nausea, vomiting and papilloedema with occasional sixth-nerve palsy. It is sometimes associated with drug therapy and tetracyclines are a well-recognized cause. Of the 76 cases reported to the Australian Adverse Drug Reactions Committee (ADRAC) over the past 30 years, 32 have been associated with minocycline.

All of these 32 patients were young, ranging in age from 12 to 30 (median: 16) years, and almost all were taking long-term minocycline for acne. Most (28) were female. The time to onset ranged from two weeks to 18 months with a median of approximately 2 months. There was also one case in which the patient developed the condition one day after she was switched from doxycycline to minocycline. The majority of the cases reported to ADRAC had recovered after minocycline was withdrawn but recovery was often prolonged, taking from 2 to 12 weeks in most cases. In those cases where treatment was reported, lumbar puncture, acetazolamide and corticosteroids were used. There were also cases where the patient had not recovered at the time the report was
submitted. Some of the reports described the use of multiple lumbar punctures, one patient required prolonged hospitalization and another a lumbo-peritoneal shunt. In one patient, lower nasal quadrantanopia persisted after 6 months (1).

ADRAC has previously drawn attention to this association but with 3 cases reported in the past 6 months, a reminder is timely (2). The possibility of drug-induced benign intracranial hypertension should be considered in any young patient presenting with persistent unexplained headache, and women taking minocycline appear to be at particular risk (3).

References


Neuropsychiatric events: celecoxib and rofecoxib

Acute neuropsychiatric reactions are known to occur with the nonselective NSAIDs, and are mentioned in the product information for these medicines. It appears that they may also be a class effect for the selective COX-2 inhibitors, including celecoxib (Celebrex®) and rofecoxib (Vioxx®).

More commonly reported acute neuropsychiatric reactions:

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>celecoxib</th>
<th>rofecoxib</th>
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</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Somnolence</td>
<td>22</td>
<td>6</td>
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<tr>
<td>Insomnia</td>
<td>21</td>
<td>6</td>
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<tr>
<td>Hallucination</td>
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<td>Depression</td>
<td>18</td>
<td>3</td>
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<td>Abnormal thinking/</td>
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<tr>
<td>impaired concentration</td>
<td>15</td>
<td>4</td>
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<tr>
<td>Agitation</td>
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<td>3</td>
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<tr>
<td>Abnormal dreaming/</td>
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<tr>
<td>nightmares</td>
<td>10</td>
<td>3</td>
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<tr>
<td>Amnesia</td>
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</table>

The Australian Adverse Drug Reactions Committee (ADRAC) has received 142 reports of acute neuropsychiatric reactions associated with celecoxib and 49 with rofecoxib. These report numbers have been calculated after exclusion of psychiatric events which might have been associated with other events such as a hypersensitivity reaction or hyponatraemia.

In many cases the onset of the reaction was dramatic. The event occurred within 24 hours of the first dose in 36 cases with celecoxib and in 14 cases with rofecoxib. In 12 and 4 cases, respectively, the reaction recurred with re-exposure to the drug. In one report marked restlessness was said to occur an hour and a half after taking celecoxib on three occasions, and in another vivid dreams developed on the nights that celecoxib was taken.

Prescribers should consider warning patients of the possibility of an acute neuropsychiatric reaction when celecoxib or rofecoxib are prescribed.


Linezolid: peripheral neuropathy

Linezolid (Zyvox®) is a new antibiotic indicated for the treatment of suspected or proven infections due to organisms resistant to multiple classes of antibiotics. The Australian Adverse Drug Reactions Committee (ADRAC) has received 4 reports of peripheral neuropathy in patients who had taken linezolid for 6–9 months (1). In no case had the peripheral neuropathy resolved at the time of reporting. In the clinical trials which supported registration exposure was for no longer than 28 days (2). The risk of persistent peripheral neuropathy should be borne in mind when considering use beyond 28 days (2).

References

Zonisamide and visual hallucinations

Zonisamide is a broad-spectrum anti-epileptic drug used to treat various types of seizures. Although visual hallucinations have not been reported as an adverse effect of this agent, the following article extracted from Pharmacotherapy (1) describes three patients who experienced complex visual hallucinations and altered mental status after zonisamide treatment was begun or its dosage increased. All three had been diagnosed earlier with epilepsy, and their electroencephalogram (EEG) findings were abnormal. During monitoring, visual hallucinations did not correlate with EEG readings, nor did video recording capture any of the described events. None of the patients had experienced visual hallucinations before this event. The only recent change in their treatment was the introduction or increased dosage of zonisamide. With either discontinuation or decreased dosage of the drug, the symptoms disappeared and did not recur.

Zonisamide is one of the new anti-epileptic drugs. It was used first in Japan but is now widely available for pharmacoresistant seizures, such as primary generalized seizures, complex partial seizures, infantile spasms, and myoclonic seizures (2–5). The principal adverse effects of the drug are drowsiness, dizziness, anorexia, urolithiasis, and headache. Cognitive dysfunction, diplopia, psychosis, and behavioural abnormalities also have been reported (6, 7). Isolated complex visual hallucinations have not yet been reported, however, three patients developed this side effect during treatment with zonisamide. None of the three had experienced previous psychiatric disturbances before zonisamide was begun or its dosage increased.

Complex visual hallucinations have been identified as an adverse reaction to various anti-epileptic drugs, such as carbamazepine, phenytoin, benzodiazepines, and valproic acid (9–11). Reports of zonisamide-associated behavioural deterioration and psychotic episodes are increasing (12, 13).

Zonisamide has a broad anti-epileptic profile, which may be mediated by an effect on voltage-sensitive sodium channels or voltage-dependent T-type calcium currents (3, 6). The drug also appears to modulate inhibition mediated by gamma aminobutyric acid. Indirectly, it may cause an increase in dopamine transmission (12, 13). Two neurotransmitters — serotonin and acetylcholine — which are implicated in the pathogenesis of visual hallucinations, are concentrated in the visual cortex and visual thalamic nuclei.

One hypothesis is that an alteration of cholinergic-serotonergic interactions in these areas may result in complex visual hallucinations (8). Changes in this pathway may cause losses of direct cortical input to the cortical association area, or may increase thalamic inhibition mediated by gamma-aminobutyric acid. These actions, as well as increases in dopamine transmission, may demonstrate zonisamide’s multiple modes of action related to hallucination pathogenesis. Clinicians need to be aware of possible complications associated with zonisamide.

References


**Salmeterol study halted**

United States of America — The Food and Drug Administration (FDA) has announced an interim analysis of a large safety study of the approved asthma drug salmeterol xinafoate (Serevent® Inhalation Aerosol), a beta₂-receptor agonist. It has been suggested that the drug may be associated with an increased risk of life-threatening asthma episodes or asthma-related deaths, particularly in some patients.

The interim analysis did not show a statistically significant result for the primary endpoint — a combination of respiratory-related deaths or intubations (or ventilatory failure). There was a trend, however, towards increases in asthma deaths and serious asthma episodes when all patients in the study were considered, though again this did not reach statistical significance. A further analysis of the data from the study suggested that the risk might be greater in African-American patients. Also, further analysis showed that patients not taking inhaled corticosteroids at study entry appeared to have greater risk for serious outcomes than those who were taking inhaled corticosteroids.

This study was designed to further investigate the safety of Serevent, particularly whether it might rarely cause serious asthma-related adverse events. It was begun in 1996, after FDA received post-marketing reports of several asthma deaths associated with the use of salmeterol xinafoate inhalation aerosol and following publication of studies raising concern about the regular use of short-acting and long-acting beta agonists, including Serevent®. Because asthma patients can sometimes suffer sudden, serious, life-threatening episodes of bronchospasm as a consequence of their disease, the deaths and serious adverse events reported could neither be clearly attributed to use of this product, nor excluded as a cause.

The manufacturer of Serevent® Inhalation Aerosol, has notified investigators that it is stopping this study, mostly due to difficulties in enrolment and the likelihood the study would not give a clear result, even if fully enrolled. The Data Safety Monitoring Board overseeing this trial conducted the interim data analyses. Approximately 26 000 subjects, representing more than 4.3 million patient-days of exposure to the drug, had participated in the study. The study was intended to enrol 60 000 patients.

Salmeterol xinafoate inhalation aerosol was approved in 1994 to treat asthma, and was later extended for treatment of chronic obstructive pulmonary disease (COPD).

FDA is particularly interested in further evaluating the question of whether certain patients may be at a greater risk for rare, but potentially serious adverse events due to salmeterol xinafoate and other related drugs.

FDA emphasizes that based on available data, the benefits of salmeterol xinafoate for the asthma population continue to outweigh the risks and that the serious adverse events reported in the trial were rare. FDA strongly advises patients that they should NOT stop taking salmeterol xinafoate or any other medication for asthma or COPD without first talking to their physicians. Abruptly stopping drugs for the treatment of asthma and COPD can result in serious exacerbations of these diseases that could be life-threatening. FDA further emphasizes that all asthma drugs, including Serevent, should be a given as a part of a comprehensive treatment plan that takes into account the patient’s asthma severity and fully educates the patient in the disease and its proper treatment.

An estimated 16 million patients in the USA now have asthma and the number of asthmatics has increased significantly in recent decades.


**Labelling and manufacturing of dietary supplements**

The Food and Drug Administration has proposed a new regulation to require current good manufacturing practices (cGMPs) in manufacturing, packing and holding of dietary supplements. The proposed rule would establish standards to ensure that dietary supplements and dietary
ingredients are not adulterated with contaminants or impurities, and are labelled to reflect the active and other ingredients in the product.

This proposed rule includes requirements for designing and constructing physical plants, establishing quality control procedures, and testing manufactured dietary ingredients and dietary supplements. It also includes proposed requirements for maintaining records and for handling consumer complaints related to cGMPs.

Under the cGMP proposal, manufacturers would be required to evaluate the identity, purity, quality, strength, and composition of their dietary ingredients and dietary supplements. FDA is soliciting comments from the public and industry on this proposed regulation.

Reference: http://www.fda.gov

Dietary supplements containing ephedra

The US Department of Health and Human Services (HHS) has announced a series of measures concerning dietary supplements containing ephedra.

On the basis of new evidence in the medical literature and adverse event reports, there are reasons for heightened concern that dietary supplements containing ephedra may present a significant and unreasonable risk of illness and injury. The Food and Drug Administration will immediately solicit comments and execute a series of actions against ephedra products, particularly those making unsubstantiated claims about sports performance enhancement.

In addition, FDA proposes a warning label for all ephedra-containing dietary supplements. The proposed label warns about the risks of serious adverse events, including heart attack, seizure, stroke, and death; cautions that the risk can increase with the dose, with strenuous exercise, and with other stimulants such as caffeine; specifies certain groups (such as women who are pregnant or breast feeding) who should never use these products; and lists other conditions, such as diseases and the use of certain medications, that rule out the use of ephedrine alkaloids.

Once the 30-day comment period has ended, FDA will analyse the comments and publish its conclusions about the most appropriate approach to reducing the risk of using dietary supplement products containing ephedrine alkaloids.

Ephedra is a naturally occurring substance derived from the Chinese herbal Ma Huang. Its principal active ingredient is ephedrine, which when chemically synthesized is regulated as a drug. While products containing natural ephedrine alkaloids have long been used to treat certain respiratory symptoms in traditional Chinese medicine, in recent years they have been extensively promoted and used with the goals of aiding weight loss, enhancing sports performance, and increasing energy.

In addition, evidence is accumulating about potentially serious safety problems following the use of ephedra-containing products. A recent study has concluded that ephedra is associated with higher risks of mild to moderate side effects such as heart palpitations, psychiatric and upper gastro-intestinal effects, and symptoms of autonomic hyperactivity such as tremor and insomnia, especially when it is taken with other stimulants.

Moreover, its review of some 16 000 adverse event reports revealed two deaths, four heart attacks, nine strokes, one seizure, and five psychiatric cases involving ephedra in which the records appeared thorough and no other contributing factors were identified. However, the study recognized that such case studies are a weak form of scientific evidence. Other unmeasured factors may have contributed, and such serious adverse events are likely to happen (albeit at very low rates) among the millions of users of ephedra anyway. The study also identified other such events potentially associated with ephedra, in which other factors may have contributed to the adverse events or in which records were inadequate.

Reference: HHS News, PO3-13, 28 February 2003

Topical use of Lindane

The US Food and Drug Administration (FDA) has issued a Public Health Advisory concerning the use of topical formulations of Lindane® lotion and lindane® shampoo (gamma-hexachlorocyclohexane) for the treatment of scabies and lice. In addition:

- The boxed warning now emphasizes that it is a second-line treatment, updates information about its potential risks especially in children.
and adults weighing less than 110 pounds, and reminds practitioners that reaplication of Lindane lotion or Lindane shampoo is not the appropriate treatment, if itching continues after the single treatment.

• Lindane product package sizes will be limited to 1 and 2 ounces in order to minimize the potential for patients to apply the product in excess and to minimize reaplication of Lindane. Pharmacists should dispense a quantity sufficient for a single treatment, not to exceed 2 fluid ounces.

• A Medication Guide, designed to inform patients of the risks of Lindane products and provide instructions for appropriate use of the drugs, must now be dispensed by the pharmacist with each new prescription.

**Second-line treatment**
Lindane (gamma-hexachlorocyclohexane) is approved for topical treatment of pediculosis and scabies in patients who have either failed to respond to adequate doses, or are intolerant of, other approved therapies. Lindane has been on the market since 1951, but was labelled as second-line therapy in 1995 because there are safer alternative treatments that should be used first.

**Current issues**
FDA has determined that Lindane products have benefits that outweigh risks when used as directed. Most serious adverse events reported in association with Lindane products have been due to misuse. However, there have been rare case reports of serious reactions with apparently normal use. These reports highlight the need to emphasize the potential toxicity of Lindane in the product labels and educate healthcare providers and patients about the risks and how to minimize them, as well as to develop mechanisms to facilitate safe use once the drug is dispensed to patients. These mechanisms include having Lindane products available only in small packaged amounts to avoid excess application and requiring that the Medication Guide be given to the patient by the pharmacist with each new prescription.

**Current safety information**
The adverse events of concern* for Lindane are systemic events due to absorption of this lipophilic drug following topical application. The majority of events occurred in patients with contraindications to the use of Lindane, in patients who used the medication in excessive amounts, or in those who misused the Lindane product. Of the adverse event cases in the FDA database with a serious outcome (hospitalization, disability or death), only 20% used Lindane according to the directions in the label. All other patients did not use Lindane according to directions in the label. Most commonly, patients often reapplied Lindane because of continued itching after the treatment, either on their own volition or at their doctor’s recommendation.

Three deaths due to Lindane use have been confirmed, although 17 deaths have been reported associated with Lindane use. The three confirmed deaths all included use of Lindane not in accordance with the label, including multiple topical applications or oral ingestion. Lindane toxicity was confirmed by autopsy in a child, and was diagnosed in an adult. The third death occurred in an adult who ingested Lindane for suicide purposes.

Of the remaining 14 deaths associated with Lindane, but not confirmed, there were 4 children, 9 adults and 1 patient of unknown age. All of these deaths occurred when Lindane was applied topically. In 9 cases, use was not in accordance with the label. Scabies and head and/or pubic lice were the predominant indications for use.

**Neurological risks**
The risk of neurologic side effects associated with Lindane is known from clinical trials, spontaneous post-marketing reporting data and literature reports. These side effects have ranged from dizziness to seizures. In post-marketing reports, neurologic side effects occurred in patients who misused Lindane, as well as in patients who used Lindane according to labelled instructions. Among the adverse event reports in the FDA database, 70% reported neurologic events including seizure, dizziness, headache and paraesthesia.

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* Safety information for Lindane comes from the FDA's Adverse Event Reporting System (AERS), which is derived from spontaneous adverse event reports through FDA's MedWatch Program and literature reports submitted to the Agency. Rates of adverse events cannot be calculated from this system and underreporting is presumed, especially for older products like Lindane Lotion and Shampoo.
Extreme caution in young and elderly

Lindane is contraindicated for use in neonates and should be used with extreme caution in children and in individuals weighing less than 50 kg (110 lbs). Among adverse event reports in which the outcome was serious (resulted in hospitalization, disability or death), the very young and the elderly appeared to be more susceptible to Lindane’s adverse effects and had worse outcomes.

Animal studies have demonstrated that younger animals are more susceptible to the neurologic side effects seen with Lindane use. In addition, smaller children have a larger body surface to volume ratio that may result in proportionately larger risk of systemic exposure. For this reason, Lindane has long been contraindicated for use in neonates. It is not known whether the developing nervous system of children also increases their susceptibility to neurologic toxicity.

Other populations at increased risk

Patients who have conditions, such as HIV infection, or take certain medications that may lower the seizure threshold should be prescribed Lindane with caution. They may be at greater risk for serious adverse events. The new Lindane label lists examples of some of these conditions and medications. The label also highlights special precautions for use of Lindane in women who are breastfeeding infants.

There are case reports of neurologic adverse events in nursing home patients treated with Lindane. Factors that may have increased their susceptibility to these adverse events include concomitant medications, underlying medical conditions, and advanced age. Special consideration should be given prior to treating this population with Lindane, even if they are greater than 50 kg.

Conclusion

Lindane products should be prescribed carefully, and quantities prescribed should be limited to amounts for a single application. Patients are at risk for serious neurologic adverse events, and even death, particularly with early retreatment. It is not known how soon after administering one dose of Lindane that a second dose can be safely administered. Post-treatment itching is common, especially in the treatment of scabies and does not necessarily indicate treatment failure.

The instructions for Lindane use have been clarified in the products’ professional labels and in the Medication Guides, which by law must be dispensed with all prescriptions of lindane. Because most of the serious adverse events reported have been because of misuse of Lindane Lotion and Lindane Shampoo, it is very important that patients understand the importance of using this medication in a manner consistent with product labelling.

The FDA wants healthcare providers to be aware of this new safety information and the changes that have occurred in the label for topical Lindane Lotion and Lindane Shampoo prescribed for the treatment of scabies and lice. Healthcare providers should consider this new safety information when deciding whether to prescribe Lindane Lotion or Lindane Shampoo for patients who may be at risk for serious adverse drug sequelae.

Reference: FDA Public Health Advisory, 28 March
Essential Medicines

Use of praziquantel in pregnant and lactating women

Praziquantel, the drug of choice for the treatment of all types of schistosomiasis, was first released under a patent by Bayer (Leverkusen, Germany) in 1979 and at that time underwent the mandatory toxicology testing. However, despite few data to suggest a potentially adverse outcome, this drug was never tested on pregnant or lactating women prior to its release. This resulted in the drug being listed as a pregnancy category B drug, which is presumed safe based on animal studies, but one for which caution should be used when given to pregnant women. With regard to lactating women, the advice was to cease breast feeding for 72 hours following treatment to eliminate potential toxicity to the infant. This has resulted operationally in the exclusion of most pregnant and lactating women from national treatment campaigns and even the exclusion of adolescent girls from mass deworming programmes. As a result, the majority of women of childbearing age living in endemic countries have been left untreated or their treatment has been significantly delayed because they may be pregnant or lactating for a great part of their lives.

In an upcoming issue of Acta Tropica, the risk benefit of this issue is discussed in detail (1). In addition, a WHO informal consultation was convened with representation from the pharmaceutical industry, WHO, public health officials and international experts (2). Three main areas of evidence were reviewed: (i) experimental animal studies; (ii) human toxicology data; and (iii) a risk/benefit analysis of the detrimental impact of the disease versus the theoretical toxicity of the drug on the mother and her child.

The evidence was conclusive. Praziquantel may be considered the safest of all anthelmintic drugs and forms the backbone for all programmes to control schistosomiasis. The risks from praziquantel to either pregnant women or unborn or nursing children are exceedingly small — if they exist at all. In contrast, little doubt exists that both the mother and her unborn child suffer morbid sequels from schistosomiasis, some of which are irreversible. Moreover, the fact that pathology can develop more rapidly in pregnant women than previously thought, means that treatment delays are likely to result in even more serious outcomes (2).

Both the article and the WHO informal consultation concluded that not only should pregnant and lactating women be treated, but that some effort should be made to ensure inclusion of this vulnerable group in any national deworming efforts. This is an important change of policy and one with significant implications for deworming programmes (3).

References

1. Olds, G.R. Administration of praziquantel to pregnant and lactating women. Special Issue: Action starts now to control disease due to schistosomiasis and soil-transmitted helminthiasis. Acta Tropica, (In press.)


Benzimidazoles: use in children

The prevalence and intensity of infection with soil-transmitted helminths tends to be low in children aged less than 24 months. Nevertheless, there is growing evidence that infection detrimentally affects their growth and development. This age group of children has so far been excluded from regular deworming campaigns.

Recently, a WHO informal consultation was convened to reassess the use of the benzimidazole drugs — albendazole and mebendazole — for use in this age group. Levamisole and pyrantel, the other two drugs on the WHO Model List of Essential Medicines to treat soil-transmitted helminths, were not discussed because their original manufacturers did not indicate that they should be withheld from children less than 24 months of age.
A review of available data on health benefits of treating soil-transmitted helminth infections in these young children concluded that treatment reduced the likelihood of growth stunting and favourably influenced nutritional and cognitive outcomes. The conference also reviewed human and animal toxicological data and concluded that in children as young as 12 months there are no reasons for exclusion from treatment with albendazole or mebendazole according to existing literature and company drug information (1). Hence, a recommendation was made that children from one year old onwards should be included in systematic deworming programmes. The meeting agreed on a reduced initial dose of 200 mg of albendazole, and the usual 100 mg twice a day for three days or the single dose of 500 mg of mebendazole, for children aged 12–24 months.

For children less than 12 months of age, because they are less likely to be infected and there is a marked paucity of safety data, no new recommendations were made for this age group (2).

References

Praziquantel ‘dose pole’ for large scale deworming

The usefulness of dose poles, used to decide the appropriate drug dose on the basis of people’s height instead of their weight, has been demonstrated in the Onchocerciasis Control Programme in West Africa, where it has been used extensively for ivermectin administration. The same type of dose pole has now been developed for the administration of praziquantel in sub-Saharan Africa and validated in 12 data sets from ten African countries, totalling 25 688 people.

Of the 25 688 individuals in the data sets, 1055 (or 4.1%) had a height that did not fit the interval identified by the pole (110–178 cm). Of the remaining 24 633 people, 81.6% would have received a dose of praziquantel between 40mg/kg and 60 mg/kg, and 98% a dose between 30mg/kg and 60 mg/kg, had the number of tablets been determined with the dose pole. The dose pole performed particularly well in school age children, where 84.7% would have received a dose of praziquantel between 40mg/kg and 60 mg/kg, and 98.6% a dose between 30mg/kg and 60 mg/kg (1).

For the control of morbidity due to schistosomiasis and soil-transmitted helminthiasis, WHO currently recommends that good quality anthelmintic drugs, including praziquantel, be available at all levels of the health care system in endemic areas, and that groups at a high risk of morbidity should have access to regular treatment. Regular deworming, particularly in school age children, will help to avoid the worst effects of infection even if there is no improvement in safe water supply or sanitation. Treatment with any of the anthelmintic drugs on the WHO Model List of Essential Medicines (albendazole, levamisole, mebendazole, or pyrantel for soil-transmitted helminths, and praziquantel for all types of schistosomiasis) is safe, even when given to uninfected children. There is therefore no need to examine each child for the presence of worms. Individual screening offers no safety benefits. And it is not cost-effective; costing four to ten times more than the anthelmintic treatment itself. The WHO recommendations on how frequently to deliver targeted treatment to high risk groups in different endemic situations have recently been revised (2).

It is expected that the newly developed praziquantel dose pole will greatly facilitate the delivery of regular treatment in endemic areas, particularly to school age children, and help to consolidate large-scale control efforts (3).

References
Poor access to praziquantel at the peripheral health care level

The price of anthelminthic drugs has plummeted over the past few years and this is particularly true for praziquantel. Praziquantel can now be delivered to patients in peripheral health care structures for less than US$ 0.10 per 600 mg tablet, meaning that an average treatment for schistosomiasis costs approximately US$ 0.30 (40 mg/kg, children and adults confounded).

Despite its low cost, access to praziquantel at the peripheral health care level remains generally poor. This clearly illustrates that an affordable price is only one of the factors contributing to good access to essential medicines. The other factors are, generally: a reliable system supplying drugs to peripheral health care structures, rational use at that level, and a sustainable financing system.

Because of the focal nature of schistosomiasis, low priority is usually accorded to the inclusion of praziquantel in the basic package of essential medicines to be delivered to the peripheral level. Yet it is the drug of choice for schistosomiasis, a disease that has irreversible consequences if not treated early. Moreover, there is still a tendency to seek microscopic confirmation of the diagnosis, requiring a referral of the patient to the district level in many instances. This can considerably increase the cost of treatment and compromise access (1). As praziquantel is a safe drug, symptom-based treatment should be the rule in first-line health care facilities in endemic areas. Today, with cost-recovery mechanisms in place, the financial burden on the health system of such symptom-based treatment is minimal.

For the control of morbidity due to schistosomiasis and soil-transmitted helminthiasis, WHO currently recommends that good quality anthelminthic drugs should be available at all levels of the health care system in endemic areas and that groups at a high risk of morbidity — especially school age children — have regular access to treatment (2). As part of this ‘minimal’ package, it is essential that people who are ill due to schistosomiasis have easy access to treatment close to their homes.

References


New class of HIV treatment approved

United States of America — The Food and Drug Administration (FDA) has announced the accelerated approval of enfuvirtide (Fuzeon®) for use in combination with other anti-HIV medications to treat advanced HIV-1 infection in adults and children aged 6 years and older (1).

Enfuvirtide, an injectable fusion inhibitor, interferes with the entry of HIV-1 into cells by inhibiting the fusion of viral and cellular membranes. This inhibition blocks the virus’ ability to infect certain components of the immune system. By affecting viral spread in a different way from existing medications, enfuvirtide helps reduce viral load and slows HIV progression in patients who have developed resistance to currently available medications.

Since HIV must be treated with a combination of medications to be effective, enfuvirtide can be used as part of a medication regimen in patients for whom there are limited options. Enfuvirtide should only be used in patients who have previously used other anti-HIV medications and have ongoing evidence of viral replication.

FDA based its accelerated approval of enfuvirtide on an analysis of data from two ongoing clinical trials involving approximately 1000 patients. The long-term effects of enfuvirtide are not yet known but are being evaluated through ongoing studies.

The approved labelling for enfuvirtide warns physicians to carefully monitor patients for signs and symptoms of pneumonia. Although bacterial pneumonia was uncommon in clinical study participants, more patients treated with enfuvirtide developed bacterial pneumonia than did patients who did not receive enfuvirtide. Patients receiving enfuvirtide are advised to seek medical evaluation immediately if they develop signs or symptoms suggestive of pneumonia. In addition, enfuvirtide can cause both serious systemic allergic reactions and local skin reactions at the site of injection.

Local skin reactions from enfuvirtide injections are common, occur in almost all patients, and may be painful. Patients must be careful that their skin does not become infected at the site of injection.

It is estimated that enfuvirtide will cost approximately $19 000 for one year’s therapy (2). Enfuvirtide, a 36-amino acid peptide, is the most complex synthetic peptide to be produced on such a scale and its manufacturing process has set an unprecedented challenge to the manufacturers. Making it involves 106 chemical reactions compared to a typical manufacturing process of 8 to 12 steps, and uses 44 rather than the average 15 raw materials.

References
1. FDA News, P03–15, 13 March 2003

Influenza vaccine composition: Northern hemisphere

World Health organization — It is recommended that vaccines to be used in the 2003/2004 Winter season contain the following strains:

• an A/New Caledonia/20/99 (H1N1)-like strain
• an A/Moscow/10/99/(H3N2)-like strain
  (A widely-used strain is A/Panama/2007/99)
• a B/Hong Kong/330/2001-like strain
  (Currently used vaccine strains include:
  B/Shandong/7/97, B/Hong Kong/330/2001
  or B/Hong Kong/1434/2002)

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

Most of the population is likely to have been infected with influenza A(H1N1), influenza A (H3N2) and influenza B viruses. As a conse-
one dose of inactivated influenza vaccine should be immunogenic for individuals of all ages except young children. Previously unimmunized children should receive two doses of vaccine with an interval of at least four weeks between doses.

**European Union** — The Ad Hoc Influenza Working Group of the Committee for Proprietary Medicinal products (CPMP) was convened to select virus strains for the manufacture of influenza vaccines for the 2003/2004 season and has agreed that the WHO recommendations should be followed.

On the basis of cross reactivity and growth in eggs, the group agreed that for the purpose of vaccine manufacture the following strains be accepted:

- Reassortant virus RESVIR-17, which has been derived from A/Panam/2007/99 as an A/Moscow/10/99-like strain
- Reassortant virus IVR-116 which is derived from A/New Caledonia/20/99 as an A/New Caledonia/20/99-like strain
- B/Shandong/7/97, which is a B/Hong Kong/330/2001-like strain.

**References**


**New labelling for conjugated estrogens**

**United States of America** — The manufacturer of conjugated estrogens/medroxyprogesterone acetate (Prempro™) (Premphase®), and conjugated estrogens tablets (Premarin®) has informed health care professionals of new labelling changes. These state that estrogens and estrogens plus progestin therapies should not be used for the prevention of cardiovascular disease. The boxed warning for estrogen-only therapies includes this same language as well as the long-recognized advisory that estrogens increase the risk of endometrial cancer when used without a progestin.

The boxed warning also includes risk information that previously appeared in other sections of the labelling. Specifically, it states that because the Women’s Health Initiative (WHI) study reported an increased risk of myocardial infarction, stroke, invasive breast cancer, and venous thromboembolism (VTE), estrogen and estrogens plus progestin therapies should be prescribed for the shortest duration consistent with treatment goals. The boxed warning also states that because other combinations of estrogens and progestins were not studied in the WHI, in the absence of comparable data, the risks identified in the study should be assumed to be similar for all postmenopausal hormone therapy (HT) products.

The FDA is contacting other manufacturers of HT products to urge them to implement similar revisions to the prescribing information for their products.

Conjugated estrogens/medroxyprogesterone acetate and conjugated estrogens are indicated for:

- Relief of moderate to severe vasomotor symptoms associated with menopause (the primary reason women seek treatment);
- Relief of moderate to severe symptoms of vulvovaginal atrophy associated with menopause;
- Prevention of postmenopausal osteoporosis in appropriately selected patients.

When used in women without menopausal symptoms for the prevention of postmenopausal osteoporosis, HT should be used only in women at significant risk for osteoporosis in whom nonestrogen therapies have been carefully considered.


**Fibrinolytics in diabetic patients**

**European Union** — The following Position Statement has been published by the Committee for Proprietary Medicinal products (CPMP) on use of fibrinolytics in diabetic patients.

Intravenous (iv) fibrinolytic agents are indicated for the treatment of acute myocardial infarction (AMI). Patients with diabetes mellitus are at an increased risk of AMI and subsequent morbidity
and mortality, and thus clearly stand to benefit from fibrinolytic treatment. All i.v. fibrinolytic treatments currently licensed in the EU nonetheless include a contraindication or warning regarding use in patients with diabetic haemorrhagic retinopathy. Considering that in order to provide maximal benefit, fibrinolytic therapy should be administered as soon as possible after diagnosis of AMI, a full medical history and detailed medical examination including fundoscopy is often impossible.

The medical rationale for contraindication in these patients was based on a theoretically increased risk of retinal bleeding due to proliferative diabetic retinopathy, rather than on evidence from clinical trial or post-marketing findings. In this respect, the CPMP has recently undertaken a comprehensive review of published data and pharmacovigilance databases and found that the number of spontaneous and clinical trial reports of retinal haemorrhage following i.v. administration of fibrinolytic agents for the treatment of AMI is extremely small. On the other hand there is clear evidence of reduced cardiac morbidity and mortality and of a reduction in total mortality following the use of fibrinolytics in patients with AMI.

On the basis of all the data available, the CPMP concluded that the risk of intraocular haemorrhage is therefore outweighed by the increased chance of survival and reduced cardiac morbidity for the diabetic patient treated early with fibrinolytic therapy. The CPMP recommends the removal of the contraindications and warnings for use of iv fibrinolytics in diabetic patients or those with diabetic retinopathy.


Precautions for blood and urine–derived products

United Kingdom — The Committee on Safety of Medicines (CSM) has advised that gonadotropin [Metrodin High Purity (HP)] should no longer be used. Gonadotropin is used predominantly for strong stimulation of the ovary in women undergoing in vitro fertilization (IVF) or, less frequently, in women who have a hormonal deficiency leading to a failure to ovulate. More rarely, it is used to treat men with a hormonal deficiency that affects the production of sperm.

The Committee’s advice is based on the precautionary principle that products manufactured from human urine sourced from a country with one or more cases of variant Creutzfeldt-Jakob Disease (vCJD), should not be used whenever practicable. Metrodin HP is manufactured from urine sourced from Italy, and withdrawal is a purely precautionary measure following the confirmation of a case of vCJD in Italy. There are adequate supplies of alternative products and other urine-derived products on the UK market are not affected. Patients who are currently undergoing treatment with Metrodin HP should discuss with their doctors whether to switch to another product during the treatment cycle.

Due to the number of cases of vCJD that have occurred in the UK, the CSM has recommended as a precautionary measure that human blood plasma sourced from the UK not be used to prepare medicines. This precautionary principle has since been logically extended to cover any country where at least one case of vCJD has arisen. Following consideration of a publication reporting that an abnormal prion protein has been identified in urine of CJD patients, CSM advised that the same precautionary principle that is in place for plasma should apply to urine.


Gefitinib: safety measures

Japan — The Pharmaceutical Affairs Bureau has announced safety measures to be taken for use of gefitinib (Iressa) following the announcement of deaths associated with use (1).

Gefitinib is the first in a new class of epidermal growth factor receptor inhibitors targeting proteins produced only by cancer cells. It is seen as a promising new treatment for terminally ill lung cancer patients.

The new safety measures require that:

- Only experienced physicians should prescribe the drug and it should only be used in facilities able to respond to serious side effects.
- The patient should be kept under hospital surveillance for the first four weeks of therapy in the event that adverse drug reactions such as interstitial pneumonia occur.

To date, gefitinib has been administered to more than 42,000 people worldwide. Interstitial lung disease and interstitial pneumonia are known complications of many lung diseases, including advanced lung cancer. Patients and physicians should be informed of the potential risk and watch for any signs and symptoms (2).

References

Nefazodone withdrawal

Spain — Nefazodone, an antidepressant, has been marketed in Spain since 1997. Recently, as a consequence of rare but serious hepatoxic adverse reactions reported in Spain and elsewhere, the Committee on Safety of Human Use Medicines has re-evaluated the risk/benefit ratio of nefazodone (1). The Committee has concluded that, when compared with other alternative antidepressants, nefazodone presents an unfavourable risk/benefit profile.

Safety data for nefazodone were evaluated in Europe in 1999 and resulted in modification of the safety data sheet (2). In April 2002, a further review was requested taking into account worldwide data. As a result, the Committee concluded that the risk of hepatotoxicity was greater than the therapeutic advantages in view of the availability of other more effective antidepressant therapies. As a result all products containing nefazodone have been withdrawn as of 1 March 2003.

References

Amifostine: serious reactions

Spain — The Spanish Medicines Agency, in coordination with other European Union regulatory authorities, has modified the labelling and package insert for amifostine (Ethyl®) (1). Amifostine is used as a chemotherapeutic agent to (i) protect patients with solid tumours against the cumulative nephrotoxic effects of cisplatin, (ii) reduce the risk of infection associated with cisplatin (in combination with cyclophosphamide) -induced neutropenia in patients with ovarian cancer, and (iii) prevent xerostomia induced by radiotherapy in patients with (ORL) neck or head tumours (2).

During clinical trials, four of 379 patients receiving amifostine for radioprotective purposes (1%) and as chemotherapy in one in 1356 patients (0.07%) are reported to have developed a serious dermatological adverse reaction. Growing use in recent years has increased the number of adverse reactions. Up to February 2003, 35 cases of serious dermatological reactions have been reported worldwide, 24 of which were during radiation-protection use. Cases also resulted from continued use of amifostine despite signs suggesting an imminent adverse reaction.

Among cases reported were: toxic epidermal necrolysis (11), Stevens-Johnson syndrome (10), polymorphic erythema (8), toxiadermia (3) and rash (3). Four of the 35 cases were fatal.

Safety information data has been urgently modified to include recommendations on management of dermatological reactions and frequency.

The following important points are highlighted:
• The risk-benefit of amifostine continues to be favourable for the authorized indications.
• Health care professionals are requested to pay special attention to possible signs and symptoms of a serious dermatological reaction. Treatment should be interrupted if a serious dermatological reaction is suspected. Patients should be informed of possible signs and symptoms and be told to contact a physician if this should occur.
• Recommendations set out in the safety information on measures for the prevention and control of possible adverse drug reactions should be followed.

References
Sirolimus: not recommended in lung transplant

United States of America — The manufacturer of sirolimus (Rapamune®), which is indicated for the prophylaxis of organ rejection in patients receiving renal transplants, has received post-marketed reports of bronchial anastomotic dehiscence, including fatal cases, in lung transplant patients treated in combination with tacrolimus and corticosteroids.

Two centres have reported this serious adverse event in lung transplant recipients in whom this immunosuppressive regimen was initiated at the time of transplantation. At one centre, four of fifteen (4/15) patients enrolled in an investigator-sponsored study developed bronchial anastomotic dehiscence; a fatal outcome was identified in three of these four patients. The second centre reported two cases of bronchial anastomotic dehiscence, one of which was fatal.

The safety and efficacy of sirolimus as immunosuppressive therapy has not been established in lung transplant patients, and, therefore, such use is not recommended. The prescribing information for sirolimus has been updated to include new information in the boxed warnings section as follows:

Liver transplantation — Excess mortality, graft loss, and hepatic artery thrombosis (HAT)
The use of sirolimus in combination with tacrolimus was associated with excess mortality and graft loss in a study in de novo liver transplant recipients. Many of these patients had evidence of infection at or near the time of death.

Lung transplantation — bronchial anastomotic dehiscence
Cases of bronchial anastomotic dehiscence, most fatal, have been reported in de novo lung transplant patients when sirolimus has been used as part of an immunosuppressive regimen.

The safety and efficacy of sirolimus as immunosuppressive therapy has not been established in liver or lung transplant patients and therefore, such use is not recommended.

Increased susceptibility to infection and the possible development of lymphoma and malignancy, especially of the skin, may result from immunosuppression. Only physicians experienced in the use of immunosuppressive therapy and the management of transplant patients should use sirolimus. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Reference: Text of a letter from Wyeth (undated) on http://www.fda.gov/medwatch

Interferon beta-1a: strengthened labelling

United States of America — The manufacturer of interferon beta-1a (Avonex®) has informed healthcare professionals of several changes to the prescribing information.

The clinical studies section of the labelling for interferon beta-1a has been updated to include the results of a study showing efficacy in multiple sclerosis (MS) patients who had recently experienced an isolated demyelinating event and who had MRI lesions typical of MS. Additionally, to address the findings in this group of patients, the indications and usage section of the labelling has been revised accordingly.

The warning section of the safety information has been revised to include a cautionary note regarding use of interferon beta-1a in patients with depression and other severe psychiatric symptoms, and post-marketing reports of depression, suicidal ideation and/or development of new or worsening of pre-existing other psychiatric disorders, including psychosis.

New warnings added to the labelling include rare reports of anaphylaxis and other allergic reactions, and post-marketing reports of decreased peripheral blood counts, including pancytopenia and thrombocytopenia.

To address post-marketing reports of autoimmune disorders, including autoimmune hepatitis, and hepatic injury manifesting itself as elevated serum enzyme levels and hepatitis, two new subsections have been added to the precautions section.

The section on adverse reactions has been thoroughly revised and updated to reflect the combined safety data from two placebo-controlled studies, to clarify the adverse reactions most
commonly reported and associated with the use of interferon beta-1a and to include a new subsection to address safety information obtained from post-marketing reports.


**Palivizumab: prescribing information changes**

**United States of America** — At the time Palivizumab (Synagis®) was licensed, there were no observed cases of anaphylaxis. However, because of the protein nature of the product, such reactions could be anticipated and was presented as a theoretical risk statement in the Warnings section. Post licensure information based on worldwide post-marketing experience representing over 400 000 patients and 2 million doses administered have been reviewed, and a total of 2 patients with anaphylaxis have been reported. Both patients made a full recovery with appropriate therapy. Because the risk of anaphylaxis has changed from a theoretical to an actual, but very rare occurrence, the warnings section has been modified to read:

*Very rare cases of anaphylaxis (<1 case per 100,000 patients) have been reported following re-exposure to palivizumab. Rare severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure to palivizumab. If a severe hypersensitivity reaction occurs, therapy with palivizumab should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on readministration of palivizumab. If anaphylaxis or severe allergic reactions occur, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.*

Additionally, the following statement was added

*Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of palivizumab are similar in character and frequency to those after the initial five doses.*


**Epigallocatechin gallate marketing suspension**

**France** — The French Agency for Safety of Medicines has suspended the marketing authorization for Epigallocatechin gallate (Exolise®), a particularly strong phytotherapeutic extract of green tea (Camellia sinensis). It is indicated as an adjunct to weight-loss programmes and has been on the market since 1999. Since this date, 13 cases of hepatic failure, of which 4 were serious, have been reported both in France and Spain. These rare cases (approximately 1 in 100,000 packages sold) have appeared some 50 days after beginning treatment. In the majority of cases, discontinuation has led to favourable recovery, but in one case has resulted in liver transplantation.

All other green tea extract products which are synthesized normally remain unaffected by this decision.


**Pergolide mesilate: strengthened warning**

**United States of America** — During post-marketing surveillance of pergolide mesilate (Permax®), a small number of individuals have been identified as developing cardiac valvulopathy involving one or more valves. Pergolide is indicated as adjunctive treatment to levodopa/carbidopa in the management of symptoms of Parkinson disease. Of the estimated 500 000 people who have been treated with pergolide since 1989, valvulopathy has been reported in less than 0.005%.

The pathological assessment of valves that were surgically removed was consistent with valvulopathy associated with carcinoid syndrome and with the use of other ergot alkaloid drugs. In the reports made to the manufacturer, aortic, mitral and tricuspid valves were involved. In some cases the symptoms or manifestations of valvulopathy improved with cessation of pergolide therapy. Valve replacement was required in two patients. It is not known whether the fibrotic valvular changes are related to retroperitoneal, pleural, or pericardial fibrosis, which are very rare but recognized adverse effects seen with pergolide mesilate.
The Warnings section of the US Package Insert has been modified as follows:

Serous Inflammation and Fibrosis — There have been rare reports of pleuritis, pleural effusion, pleural fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy involving one or more valves, or retroperitoneal fibrosis in patients taking pergolide. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of pergolide. Pergolide should be used with caution in patients with a history of these conditions, particularly those patients who experience the events while taking ergot derivatives. Patients with a history of such events should be carefully monitored and with appropriate radiographic and laboratory studies.

WHO's new bookshop

The World Health Organization is now providing an electronic bookshop facility on http://www.who.int/dsa. An online electronic catalogue gives information on WHO publications and other information support systems such as CD-ROM and video. It has a search facility which links up to health related subjects, new publications, catalogues, brochures and the WHO website. Books can be ordered online and links are available to WHO sales agents and depository libraries.

Other communications and orders continue to be handled through e-mail on bookorders@who.int or by mail: Distribution, Sales and Marketing, World Health Organization, 1211 Geneva 27, Switzerland.

WHO monographs on medicinal plants

Volume Two of Monographs on Selected Medicinal Plants has now been published by WHO and includes an additional collection of 30 monographs to complement those of Volume 1. The monographs provide scientific information on the safety, efficacy and quality aspects of widely used medicinal plants. Their purpose is to facilitate appropriate use and provide model information to assist national authorities in developing monographs or formularies for herbal medicines.

A detailed botanical description is provided of each medicinal plant and crude drug. Active chemical constituents and information on geographical distribution are given to assist with quality assurance and a selection of vernacular names from individual countries is included to assist identification. A description of the clinical applications of the plant material follows with pharmacological information, contraindications, warnings, precautions, adverse reactions and dosage. A cumulative index is also included.

As a comprehensive scientific reference, the monographs are intended to promote international harmonization and facilitate exchange of information on herbals. They will also be useful as a valuable scientific reference for physicians, practitioners, pharmacists, manufacturers, research scientists, and the general public.

WHO Monographs on Selected Medicinal Plants is available from: bookorders@who.int or Distribution, Sales and Marketing, World Health Organization, 1211 Geneva 27, Switzerland. ISBN 92 4 154537 2

International Pharmacopoeia: Volume 5

The latest edition of The International Pharmacopoeia: Tests and General Requirements for Dosage Forms. Quality Specifications for Pharmaceutical Substances and Tablets describes methods and procedures for the quality control of pharmaceutical substances and dosage forms, including a special section on quality control of anti-malarials, with monographs on most artemisinin derivatives known to date. The International Pharmacopoeia gives priority to medicines for illnesses affecting developing country populations and those listed on the WHO Model List of Essential Medicines.

The monographs can be used in any country or setting. For this purpose, they are designed to cater for both high-technology methods of testing or, when these are not available, for alternative methods which are less technically demanding. Publication of The International Pharmacopoeia is aimed to help regulatory authorities, health services and manufacturers assure the quality of medicines and eliminate substandard products.

The following topics are also included: Tests, methods, and general requirements; Monographs for pharmaceutical substances; Monographs for tablets; Monographs for antimalarial drugs; List of reagents, test solutions, and volumetric solutions; General requirements for dosage forms; Ophthalmic preparations; Suppositories; Tests for dosage forms; Disintegration test for suppositories;
Dissolution test for solid oral dosage forms; Test for extractable volume for parenteral preparations; Microbial purity of pharmaceutical preparations; Test for bacterial endotoxins; Test for sterility of non-injectable preparations; Visual inspection of particulate matter injectable preparations.


HIV treatment newsletter

HIV and AIDS Treatment in Practice is a free-of-charge e-mail newsletter which has been launched for doctors, nurses and health care workers. The newsletter is published by a UK information charity. A voluntary advisory panel consisting of researchers and representatives from public, private and nongovernmental organizations will guide development of the information.

Each issue will review one major topic in HIV and AIDS treatment and will contain specialist comment. All articles are medically reviewed to ensure accuracy, balance and relevance.


Fixed-dose combinations for tuberculosis drugs

Ensuring that people with tuberculosis complete a full course of treatment is one of the major challenges of TB control. The risk is that uninformed patients or doctors may change the regimen, avoiding one or more of the drugs they believe are not necessary (or available) leading to treatment failure or relapse. In so doing, some of the patients may develop antimicrobial resistance.

There are various strategies to prevent non-compliance, and one approach is through fixed-dose combination (FDC) tablets. Recent advances in pharmacology have now made it possible to develop quality combinations of two, three or four anti-TB drugs in a single tablet.

Prevention of drug resistance is just one of the potential benefits of FDCs. FDCs simplify administration of drugs by reducing the number of pills a patient takes each day and decreasing the risk of incorrect prescriptions — and, in particular, the risk of confusion by care-givers. Drug procurement — including stock management, shipping, and distribution — is simplified.

The World Health Organization has published an Operational Guide for National Tuberculosis Control Programmes on the Introduction and Use of Fixed Dose Combination Drugs. It provides easy-to-follow guidance on programmatic, managerial, quality and regulatory matters with practical approaches to facilitating use in a TB control programme. The guide contains minimum requirements and is not intended to replace existing requirements or practices. Approaches other than those described may also be applicable and acceptable and these should be chosen by the national tuberculosis programme. Above all, his tool will help managers understand the need to ensure bioavailability, comply with regulatory requirements and shift patients from regimens based on single-drug dosage.

Malaria: interactive self-assessment

The malaria educational site at the Royal Perth Hospital, Australia, is available in French, English and Spanish. The site contains sections on diagnosis, prophylaxis, treatment and history of malaria as well as an interactive self assessment module which is ideal for clinicians, scientists, healthcare professionals and students.

International Nonproprietary Names for Pharmaceutical Substances (INN)

Notice is hereby given that, in accordance with article 3 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances, the names given in the list on the following pages are under consideration by the World Health Organization as Proposed International Nonproprietary Names. The inclusion of a name in the lists of Proposed International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.

Lists of Proposed (1–85) and Recommended (1–45) International Nonproprietary Names can be found in Cumulative List No. 10, 2002 (available in CD-ROM only). The statements indicating action and use are based largely on information supplied by the manufacturer. This information is merely meant to provide an indication of the potential use of new substances at the time they are accorded Proposed International Nonproprietary Names. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature, these descriptors will neither be revised nor included in the Cumulative Lists of INNs.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Il est notifié que, conformément aux dispositions de l'article 3 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques les dénominations ci-dessous sont mises à l'étude par l'Organisation mondiale de la Santé en tant que dénominations communes internationales proposées. L'inclusion d'une dénomination dans les listes de DCI proposées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.

On trouvera d'autres listes de Dénominations communes internationales proposées (1–85) et recommandées (1–45) dans la Liste récapitulative No. 10, 2002 (disponible sur CD-ROM seulement). Les mentions indiquant les propriétés et les indications des substances sont fondées sur les renseignements communiqués par le fabricant. Elles ne visent qu'à donner une idée de l'utilisation potentielle des nouvelles substances au moment où elles sont l'objet de propositions de DCI. L'OMS n'est pas en mesure de confirmer ces déclarations ni de faire de commentaires sur l'efficacité du mode d'action ainsi décrit. En raison de leur caractère provisoire, ces informations ne figureront pas dans les listes récapitulatives de DCI.

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

De conformidad con lo que dispone el párrafo 3 del “Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas”, se comunica por el presente anuncio que las denominaciones detalladas en las páginas siguientes están sometidas a estudio por la Organización Mundial de La Salud como Denominaciones Comunes Internacionales Propuestas. La inclusión de una denominación en las listas de las DCI Propuestas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.

Las listas de Denominaciones Comunes Internacionales Propuestas (1–85) y Recomendadas (1–45) se encuentran reunidas en Cumulative List No. 10, 2002 (disponible sólo en CD-ROM). Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. Esta información tiene por objeto dar una idea únicamente de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos no deben incluirse en las listas recapitulativas de DCI.
# Proposed International Nonproprietary Names: List 88

Comments on, or formal objections to, the proposed names may be forwarded by any person to the INN Programme of the World Health Organization within four months of the date of their publication in *WHO Drug Information*, i.e., for List 88 Proposed INN not later than 30 September 2003.

## Dénominations communes internationales proposées: Liste 88

Des observations ou des objections formelles à l'égard des dénominations proposées peuvent être adressées par toute personne au Programme des Dénominations communes internationales de l'Organisation mondiale de la Santé dans un délai de quatre mois à compter de la date de leur publication dans *WHO Drug Information*, c'est à dire pour la Liste 88 de DCI Proposées le 30 septembre 2003 au plus tard.

## Denominaciones Comunes Internacionales Propuestas: Lista 88

Cualquier persona puede dirigir observaciones u objeciones respecto de las denominaciones propuestas, al Programa de Denominaciones Comunes Internacionales de la Organización Mundial de la Salud, en un plazo de cuatro meses, contados desde la fecha de su publicación en *WHO Drug Information*, es decir, para la Lista 88 de DCI Propuestas el 30 de septiembre de 2003 a más tardar.

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<th>Chemical Abstracts Service (CAS) registry number: Graphic formula</th>
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![Chemical structure of arundic acid](image)
acidum salcaprozicum
salcaprozic acid 8-(2-hydroxybenzamido)octanoic acid
absorption promoter

acidum salcaprozicum

acide salcaprozique acide 8-[2-hydroxybenzoyl]amino]octanoïque
promoteur d’absorption

acido salcaprózico ácido 8-(2-hidroxibenamido]octanoico
promotor de la absorción

\( \text{C}_{15}\text{H}_{21}\text{NO}_{4} \quad 183990-46-7 \)

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\text{N} & \quad \text{H} \\
\text{CO}_2 & \quad \text{H}
\end{align*}
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alvocidibum

alvocidib (-)-2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3\(R^*\),4\(S^*\))-3-hydroxy-1-methyl-4-piperidyl]-4\(H\)-chromen-4-one
antineoplastic

alvocidib

(-)-2-(2-chlorophényl)-5,7-dihydroxy-8-[(3\(R^*\),4\(S^*\))-3-hydroxy-1-méthylpipéridin-4-il]-4\(H\)-1-benzopyran-4-one
antineoplasique

alvocidib

(-)-2-(2-clorofenil)-5,7-dihidroxi-8-[(3\(R^*\),4\(S^*\))-3-hidroxi-1-metilpiperidin-4-il]-4\(H\)-cromen-4-ona
antineoplásico

\( \text{C}_{21}\text{H}_{20}\text{ClNO}_{5} \quad 146426-40-6 \)

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\text{H} & \quad \text{OHCl} \\
\text{HO} & \quad \text{H}
\end{align*}
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or enantiomer ou énantiomère o enantiómero
anatibantum

anatibant

\((2S)-N\{3-(4-carbamimidoylbenzamido)propyl\}-1\{2,4-dichloro-3\-(2,4-dimethyl-8-quinolinoxy)methyl\}phenylsulfonyl\}pyrrolidine-2-carboxamide

bradykinin B2 receptor antagonist

anatibant

\((2S)-N\{3-(4-carbamimidoylbenzoyl)amino\}propyl\}-1\{2,4-dichloro-3\-(2,4-diméthylquinoléin-8-yl)oxy\}méthyl\}phényl\}sulfonil\}pyrrolidine-2-carboxamide

antagoniste du récepteur B2 de la bradykinine

anatibant

\((2S)-N\{3-(4-carbamimidoylbenzamido)propil\}-1\{2,4-dicloro-3\-(2,4-dimetilquinolein-8-iloxi)metill\}fenil\}sulfonil\}pirrolidina-2-carboxamida

antagonista de los receptores B2 de bradiquinina

\(\text{C}_{34}\text{H}_{36}\text{Cl}_{2}\text{N}_{6}\text{O}_{5}\text{S}\)

209733-45-9

ardenerminum

ardenermin

B-lymphocyte stimulator-(134-285)-peptide

immunostimulant

ardénermine

peptide-(134-285)-stimulateur du lymphocyte-B humain

immunostimulant

ardenermina

péptido-(134-285)-estimulante del linfocito-B humano

inmunoestimulante

\([\text{C}_{770}\text{H}_{1205}\text{N}_{193}\text{O}_{232}\text{S}_{5}]_{6}\)

305391-49-5

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\text{YTDKTYAMGH} & \text{LIOQKKVHVF} & \text{GDELSLVTLF} & \text{RCIQMPETEL} \\
\text{PNNSCYSAGI} & \text{AKLEEGDELQ} & \text{LAIPRENAQI} & \text{SLGDVTFFG} \\
\text{ALKLL}
\end{array}
\]
**arimoclomolum**
arimoclomol

$N$-[(2$R$)-2-hydroxy-3-(1-piperidyl)propoxy]pyridine-3-carboximidoyl chloride, 1-oxide

*symptomatic antidiabetic agent*

**arimoclomol**

1-oxyde du chlorure de $N$-[(2$R$)-2-hydroxy-3-(pipéridin-1-yl)propoxy]pyridin-3-carboximidoyle

*antidiabétique à action symptomatique*

**arimoclomol**

1-óxido del cloruro de (Z)-$N$-[2$R$]-2-hidroxi-3-(1-piperidil)propoxi]piridina-3-carboximidoilo

*antidiabético de acción sintomática*

\[C_{14}H_{20}ClN_{3}O_{3}\]

289893-25-0

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**aselizumabum**

aselizumab


*immunomodulator*

**asélizumab**

immunoglobuline G4, anti-(sélectine L) (chaîne lourde de l’anticorps monoclonal de souris HuDreg-55 humanisé), dimère du disulfure avec la chaîne légère de l’anticorps monoclonal de souris HuDreg-55 humanisé

*immunomodulateur*

**aselizumab**

inmunoglobulina G4, anti-(selectina L) (cadena pesada del anticuerpo monoclonal humanizado de ratón HuDreg-55), dimero del disulfuro con la cadena ligera del anticuerpo monoclonal humanizado de ratón HuDreg-55

*inmunomodulador*

395639-53-9
asoprisnili ecamas
asoprisnil ecamate
11β-[4-[(E)-(ethylcarbamoyloxyimino)methyl]phenyl]-17β-methoxy-17α-(methoxymethyl)estra-4,9-dien-3-one
progesterone receptor modulator

écamate d’asoprisnil
ecamate d’asoprisnil
modulateur des récepteurs à la progestérone

ecamato de asoprisnilo
ecamato de asoprisnilo
modulador del receptor de progesterona

C_{31}H_{40}N_{2}O_{5} 163883-88-3

ataciguatum
ataciguat
5-chloro-2-[[5-chloro-2-thienyl]sulfonylamino]-N-[4-(morpholin-4-ylsulfonyl)phenyl]benzamide
vasodilator

ataciguat
5-chloro-2-[[[5-chlorothiophén-2-yl]sulfonyl]amino]-N-[4-(morpholin-4-ylsulfonyl)phényl]benzamide
dilatateur

ataciguat
5-cloro-2-[[5-cloro-2-tienil]sulfonilamino]-N-[4-(morfolin-4-ilsulfonil)fenil]benzamida
vasodilatador

C_{21}H_{19}Cl_{2}N_{3}O_{6}S_{3} 254877-67-3
**atazanavirum**

**atazanavir**
dimethyl (3S,8S,9S,12S)-9-benzyl-3,12-di-tert-butyl-8-hydroxy-4,11-dioxo-6-[4-(pyridyl)benzyl]-2,5,6,10,13-pentaaazatetradecanedioate antiviral

**atazanavir**
(3S,8S,9S,12S)-9-benzyl-3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-6-[4-(pyridin-2-yl)benzyl]-2,5,6,10,13-pentaaazatetradecanedioate de diméthyle antiviral

**atazanavir**
(3S,8S,9S,12S)-9-bencil-3,12-di-terc-butil-8-hidroxi-4,11-dioxo-6-[4-(2-piridill)bencil]-2,5,6,10,13-pentaaazatetradecanodioato de dimetilo antiviral

C_{38}H_{52}N_{6}O_{7} 198904-31-3

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**atocalcitolum**

**atocalcitol**
(1S,3R,5Z,7E,20R)-20-[3-(2-hydroxypropan-2-yl)benzyloxymethyl]-9,10-secopregna-5,7,10(19)-triene-1α,3β-diol vitamin D analogue

**atocalcitol**
(5Z,7E,20R)-20-[[3-(1-hydroxy-1-méthyléthyl)benzyl]oxy]méthyl]-9,10-sécoprégna-5,7,10(19)-triène-1α,3β-diol analogue de la vitamine D

**atocalcitol**
(1S,3R,5Z,7E,20R)-20-[3-(2-hidroxipropan-2-il)benciloximetil]-9,10-secopregna-5,7,10(19)-trieno-1α,3β-diol análogo de la vitamina D

C_{32}H_{46}O_{4} 302904-82-1
**barixibatum**

barixibat

11-(d-glucosamido)-N-[2-[(1S,2R,3S)-3-hydroxy-3-phenyl-2-(2-pyridyl)-1-(2-pyridylamino)propyl]phenyl]undecanamide

*bile acid absorption inhibitor*

barixibat

11-(d-glucosamido)-N-[2-[(1S,2R,3S)-3-hydroxy-3-phenyl-2-(2-pyridyl)-1-(2-pyridylamino)propyl]phenyl]undecanamide

**inhibiteur de la réabsorption des sels biliaires**

barixibat

{N-[2-[(1S,2R,3S)-3-fenil-3-hidroxi-2-(piridin-2-il)-1-(piridin-2-ilamino)propil]fenil]-11-(d-glucosamido)}undecanamida

**inhibidor de la reabsorción de sales biliares**

C_{42}H_{55}N_{5}O_{8} 263562-28-3

**barusibanum**

barusiban

C_{4.6},S'-ciclo[N-(3-sulfanylpropanoyl)-d-tryptofil-l-isoleucil-l-alloisoleucil-l-asparaginil-l-2-aminobutanoil-N-metil-l-ornithinol]

*oxytocin antagonist*

barusiban

(4S,7S,10S,13S,16R)-N-[(1S)-4-amino-1-(hydroximetil)butil]-7-(2-amino-2-oxoetil)-16-(1H-indol-3-ylmetil)-N-metil-10-[(1R)-1-metilpropil]-13-[(1S)-1-metilpropil]-6,9,12,15,18-pentaoxo-1-thia-5,8,11,14,17-pentaazacycloicosane-4-carboxamide

*antagoniste de l’oxytocine*

barusibán

C_{4.6},S'-ciclo[N-(3-sulfanilpropanoil)-d-triptofil-l-isoleucil-l-alloisoleucil-l-asparaginil-l-2-aminobutanoil-N-metil-l-ornitino]

*antagonista de la oxitocina*

C_{42}H_{63}N_{9}O_{8}S 285571-64-4
**bertilimumab**

**bertilimumab**

**bortezomib**

**bortezomib**

**bortezomib**

**bortezomib**
cinacalcetum

**cinacalcet**

\[ N-[\{1R\}-1-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]propan-1-amine \]

*calcimimetic*

**cinacalcet**

\[ N-[\{1R\}-1-(naphtalényl-1-yl)éthyl]-3-[3-(trifluorométhyl)phényl]propan-1-amine \]

*calcimimétique*

**cinacalcet**

\[ N-[\{1R\}-1-(1-naftil)etil]-3-[3-(trifluorometil)fenil]propan-1-amina \]

*calciomimético*

\[ C_{22}H_{22}F_{3}N \]

226256-56-0

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darunavirum

darunavir

\[(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl \]

\[ N-[(1S,2R)-1-benzyl-2-hydroxy-3-(N-isobutylsulfanilamido)propyl]carbamate \]

*antiviral*

**darunavir**

\[ [(1S,2R)-3-\{(4-aminophényl)sulfonyl\}[2-méthylpropyl]amino]-1-benzyl-2-hydroxypropyl]carbamate de (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yile \]

*antiviral*

**darunavir**

\[ N-[(1S,2R)-1-bencil-2-hidroxi-3-(N-isobutilisulfanilamido)propil]carbamato de (3R,3aS,6aR)-hexahidrofuro[2,3-b]furan-3-llo \]

*antiviral*

\[ C_{27}H_{37}N_{3}O_{7}S \]

206361-99-1
** dexmethylphenidatum **

dexmethylphenidate methyl (2\(R\))-phenyl[(2\(R\))-2-piperidyl]acetate  

** sympathomimetic **

dexméthylphénidate (2\(R\))-phényl[(2\(R\))-pipéridin-2-yl]acétate de méthyle  

** sympathomimétique **

dexmetilfenidato (2\(R\))-fenil[(2\(R\))-2-piperidiil]acetato de metilo  

** simpaticomimético **

C\(_{14}\)H\(_{19}\)NO\(_2\) 40431-64-9

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** disufentonum natricum **

disufenton sodium disodium 4-((tert-butyliminomethyl)benzene-1,3-disulfonate N-oxide  

** neuroprotective agent **

disufenton sodique N-oxyde de 4-[[1,1-diméthyléthyl)imino]méthyl]benzène-1,3-disulfonate de disodium  

** neuroprotecteur **

disufentón sódico N-óxido de 4-terc-butiliminometil]benceno-1,3-disulfonato de disodio  

** neuroprotector **

C\(_{11}\)H\(_{13}\)NNa\(_2\)O\(_7\)S\(_2\) 168021-79-2

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dofequidarum

dofequidar

1-(diphenylacetyl)-4-[(2RS)-2-hydroxy-3-(5-quinoloyloxy)propyl]piperazine

antineoplastic

doféquidar

1-(diphénylacétyl)-4-[(2RS)-2-hydroxy-3-(quinoléin-5-yloxy)propyl]pipérazine

antineoplasique

dofequidar

1-(difénilacetil)-4-[(2RS)-2-hidroxi-3-(quinolein-5-iloxi)propil]piperazina

antineoplásico

C_{30}H_{31}N_{3}O_{3} 129716-58-1

and enantiomer

et énantiomère

y enantiómero

doramapimodum

doramapimod

1-[3-tert-butyl-1-(4-methylphenyl)-1H-pyrazol-5-yl]-3-[4-(2-morpholinoethoxy)-1-naphthyl]urea

immunomodulator

doramapimod

1-[3-(1,1-diméthyléthyl)-1-(4-méthylphényl)-1H-pyrazol-5-yl]-3-[4-[2-(morpholin-4-yl)éthoxy]naphtalén-1-yl]urrée

immunomodulateur

doramapimod

1-[3-terc-butil-1-(4-metilfenil)-1H-pirazol-5-il]-3-[4-(2-morfolinoetoxi)-1-naftil]urea

inmunomodulador

C_{31}H_{37}N_{5}O_{3} 285983-48-4
etiprednol dicloacetate
ethyl 17α-(dichloroacetoxy)-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate
corticosteroid, anti-inflammatory

dicloacétate d'étiprednol
17-[(dichloroacétyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diène-17β-carboxylate d'éthyle
corticostéroïde, anti-inflammatoire

dicloroacetato de etiprednol
17-[(dicloroacetil)oxi]-11β-hidroxi-3-oxoandrosta-1,4-dieno-17β-carboxilato de etilo
corticosteriode, antiinflamatorio

C24H30Cl2O6 199331-40-3

etiravirine
4-[6-amino-5-bromo-2-(4-cyanoanilino)pyrimidin-4-yloxy]-3,5-dimethylbenzonitrile
antiviral

étravirine
4-[[6-amino-5-bromo-2-[(4-cyanophényl)amino]pyrimidin-4-yl]oxy]-3,5-diméthylbenzonitrile
antiviral

etiravirina
4-[6-amino-5-bromo-2-(4-cianoanilino)pirimidin-4-iloxi]-3,5-dimetilbenzonitrilo
antiviral

C20H15BrN6O2 269055-15-4
**etriciguatum**

*etriciguat*

2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-(4-pyridyl)pyrimidin-4-amine

*vasodilator*

**étriciguat**

2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-(pyridin-4-yl)pyrimidin-4-amine

*vasodilatateur*

**etricalguat**

2-[1-(2-fluorobencil)-1H-pirazolo[3,4-b]piridin-3-il]-5-(4-piridil)pirimidin-4-amina

*vasodilatador*

\[C_{22}H_{16}FN_7\]

402595-29-3

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**fipamezolum**

*fipamezole*

4-[(2RS)-2-ethyl-5-fluorindan-2-yl]-1H-imidazole

*antiparkinsonian, \(\alpha_2\)-adrenoreceptor antagonist*

**fipamézole**

4-[(2RS)-2-éthyl-5-fluoro-2,3-dihydro-1H-indén-2-yl]-1H-imidazole

*antiparkinsonien, antagoniste \(\alpha_2\)-adrénergique*

**fipamezol**

4-[(2RS)-2-etil-5-fluoroindan-2-il]-1H-imidazol

*antiparkinsoniano, antagonista de los receptores \(\alpha_2\)-adrenérgicos*

\[C_{14}H_{15}FN_2\]

150586-58-6

---

and enantiomer

et énantiomère

y enantiómero
**gemcabenum**

gemcabene | $2,2',2',2'$-tetramethyl-6,6'-oxydihexanoic acid | *antihyperlipidaemic*

gemcabène | acide 6,6'-oxybis(2,2-diméthylhexanoïque) | *antihyperlipidémique*

gemcabeno | ácido $2,2',2',2'$-tetrametil-6,6'-dihexanoico | *antihiperlipémico*

\[
\begin{align*}
C_{16}H_{30}O_5 & \quad \text{183293-82-5} \\
\end{align*}
\]

**ibrolipimum**

ibrolipim | diethyl \{4-[(4-bromo-2-cyanophenyl)carbamoyl]benzyl\}phosphonate | *antiatherogenic*

ibrolipim | [4-[(4-bromo-2-cyanophényl)carbamoyl]benzyl]phosphonate de diéthyle | *anti-athéromateux*

ibrolipim | [4-[(4-bromo-2-cianofenil)carbamoil]bencil]fosfonato de dietilo | *antiaterogénico*

\[
\begin{align*}
C_{19}H_{20}BrN_2O_4P & \quad \text{133208-93-2} \\
\end{align*}
\]
iclaprimum

5-[(2RS)-2-cyclopropyl-7,8-dimethoxy-2H-chromen-5-ylmethyl]pyrimidine-2,4-diamine
antibacterial

iclaprime

5-[[2RS]-2-cyclopropyl-7,8-diméthoxy-2H-1-benzopyran-5-yl]methyl]pyrimidine-2,4-diamine
antibactérien

iclaprim

5-[(2RS)-2-ciclopropil-7,8-dimetoxi-2H-cromen-5-ilmetil]pirimidina-2,4-diamina
antibacteriano

C₁₉H₂₂N₄O₃ 192314-93-5

---

iosimenol

5,5'-[propanedioylbis[(2,3-dihydroxypropyl)imino]bis[N-(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide]
contrast medium

iosiménol

5,5'-[propanedioylbis[(2,3-dihydroxypropyl)imino]bis[N-(2,3-dihydroxypropyl)-2,4,6-triiodobenzène-1,3-dicarboxamide]
produit de contraste

iosimenol

5,5'-[propanedioylbis[(2,3-dihidroxipropil)imino]bis[N-(2,3-dihidroxipropil)-2,4,6-triiodobenceno-1,3-dicarboxamida]
medio de contraste

C₃₁H₃₆I₆N₆O₁₄ 181872-90-2
latidectinum

latidectin

mixture of components A₄ and A₃

component A₄:

(2α⁰S,2αE,4E,5'S,6S,6'R,7R,8E,11R,13R,15S,17αR,20R,20aR)-6'-(ethyl-2α',20-dihydroxy-5',6,8,19-tetramethyl-17-oxo-
1-[4-(methoxyacetamido)phenyl]cyclopentanecarboxylate

component A₃:

1-[4-(methoxyacetamido)phenyl]cyclopentanecarboxylate

antiparasitic

latidectine

mélange des composés A₄ et A₃

composé A₄:

1-[4-[(méthoxyacétyl)amino]phényl]cyclopentanecarboxylate de
(2αE,4E,5'S,6S,6'R,7R,8E,11R,13R,15S,17αR,20R,20aR,20bS)-6'-éthyl-20,20b-dihydroxy-5',6,8,19-tétraméthyl-17-oxo-

composé A₃:

1-[4-[(méthoxyacétyl)amino]phényl]cyclopentanecarboxylate de

antiparasitaire

latidectina

mezcla de los componentes A₄ y A₃

componente A₄:

1-[4-[metoxiacetamido]fenil]ciclopentanocarboxilato de
(2α⁰S,2αE,4E,5'S,6S,6'R,7R,8E,11R,13R,15S,17αR,20R,20aR),-6'-etil-2α',20-dihidroxi-5',6,8,19-tetrametil-17-oxo-

componente A₃:

1-[4-[metoxiacetamido]fenil]ciclopentanocarboxilato de

antiparasitario
lurasidone

\( \text{C}_{46}\text{H}_{61}\text{NO}_{11} \text{ (component } A_3) \) 371918-51-3 (component \( A_3 \))

\( \text{C}_{47}\text{H}_{63}\text{NO}_{11} \text{ (component } A_4) \) 371918-44-4 (component \( A_4 \))

\[
\begin{align*}
\text{lurasidone} & \quad (3aR,4S,7R,7aS)-2-\{(1R,2R)-2-[4-(1,2-benzothiazol-3-yl)piperazin-1-ylmethyl]cyclohexyl[methyl]hexahydro-4,7-methano-2H-isindo-1,3-dione antipsychotic} \\
\text{lurasidone} & \quad (3aR,4S,7R,7aS)-2-\{(1R,2R)-2-[4-(1,2-benzothiazol-3-yl)piperazin-1-ylmethyl]cyclohexyl[methyl]hexahydro-4,7-methano-2H-isindo-1,3-dione antipsychotique} \\
\text{lurasidona} & \quad 3aR,4S,7R,7aS)-2-\{(1R,2R)-2-[4-(1,2-benzothiazol-3-yl)piperazin-1-ylmethyl]cyclohexyl[methyl]hexahydro-4,7-methano-2H-isindo-1,3-diona antipsicótico}
\end{align*}
\]

\( \text{C}_{28}\text{H}_{36}\text{N}_{4}\text{O}_{2}\text{S} \) 367514-87-2
mantabegronum

mantabegron    (2RS)-1-(adamantan-1-ylamino)-3-phenoxypropan-2-ol
β₃-adrenoreceptor agonist (veterinary drug)
mantabégron    (2RS)-1-phénoxy-3-(tricyclo[3.3.1.1₃,₇]déc-1-ylamino)propan-2-ol
agoniste des récepteurs β₃ adrénergiques (usage vétérinaire)
mantabegrón    (2RS)-1-fenoxi-3-(triciclo[3.3.1.1₃,₇]dec-1-ilamino)propan-2-ol
agonista de los receptores β₃-adrenérgicos (medicamento veterinario)

C₁₉H₂₇NO₂  36144-08-8

matuzumabum

matuzumab    immunoglobulin G1, anti-(human epidermal growth factor receptor)
(humanized MAb 425 γ₁ chain), disulfide with humanized MAb 425 κ-chain, dimer
immunomodulator
matuzumab    immunoglobuline G1, anti-(récepteur du facteur de croissance humain de
l’épiderme) (chaîne γ₁ de l’anticorps monoclonal de souris 425 humanisé),
dimère du disulfure avec la chaîne κ de l’anticorps monoclonal de souris 425 humanisé
immunomodulateur
matuzumab    immunoglobulina G1, anti-(receptor humano del factor de crecimiento de la
epidermis) (cadena γ₁ del anticuerpo monoclonal humanizado de ratón 425),
dímero del disulfuro con la cadena κ del anticuerpo monoclonal humanizado de ratón 425
inmunomodulador

339186-68-4
mitratapidum
mitratapid

\[2-\{(2R)-\text{butan-}2\text{-yl}\}-4-\{(4-\{(2S,4R)-2-(4\text{-chlorophenyl})-2-[(4\text{-methyl-}\ 4H-1,2,4\text{-triazol-3-yl}sulfanyl]methyl}-1,3\text{-dioxolan-4-yl}]methoxy\text{phenyl}\}[\text{piperazin-1-yl}]\text{phenyl}\}-2,4\text{-dihydro-3H-1,2,4-triazol-3-one}\]

microsomal triglyceride transfer protein (MTP) inhibitor (veterinary drug)

mitratapid

\[4-\{(2S,4R)-2-(4\text{-chlorophényle})-2-[(4\text{-méthyl-}\ 4H-1,2,4\text{-triazol-3-yl}]sulfanyl]méthyl}-1,3\text{-dioxolan-4-yl}[\text{méthoxy}\text{phényl}][\text{pipérazin-1-yl}]\text{phényl}\}-2-\{(1R)-1\text{-méthylpropyl}\}-2,4\text{-dihydro-3H-1,2,4-triazol-3-one}\]
inhibiteur des protéines microsomiales de transfert des triglycerides (usage vétérinaire)

mitratapid

\[2-\{(2R)-\text{butan-2-il}\}-4-\{(4-\{(2-\text{(4-clorofenil)}-2-[(2S,4R)-(4\text{-métile-}\ 4H-1,2,4\text{-triazol-3-il}sulfanil]metil}-1,3\text{-dioxolan-4-il}]metoxi)fenil\}[\text{pipérazin-1-il}]\text{fenil}\}-2,4\text{-dihidro-3H-1,2,4-triazol-3-ona}\]
inhibidor de la proteína microsómica de transporte de triglicéridos (MTP) (medicamento veterinario)

\[
\text{C}_{36}\text{H}_{41}\text{ClN}_8\text{O}_4\text{S} \quad 179602-65-4
\]

oxeglitazarum

oxeglitazar

\[(2E,4E)-5-(7\text{-méthoxy-3,3-diméthyl-2,3-dihydro-1-benzoxépin-5-yl})-3\text{-méthylpenta-2,4-diénoïque}\]
antidiabétique

oxéglitazar

\[(2E,4E)-5-(7\text{-methoxy-3,3-dimethyl-2,3-dihydro-1-benzoxepin-5-yl})-3\text{-méthylpenta-2,4-diénoïque}\]
antidiabétique

oxeglitazar

\[(2E,4E)-3\text{-métile-}5-(3,3\text{-dimetil-7-metoxi-2,3-dihidro-1-benzoxepin-5-il})\text{penta-2,4-dienoico}\]
antidiabético

\[
\text{C}_{19}\text{H}_{22}\text{O}_4 \quad 280585-34-4
\]
posizolidum

posizolid

\( (5R)-3-(4\{1\{(2S)-2,3\text{-dihydroxypropanoyl}\}-1,2,3,6\text{-tetrahydro\text{-}4\text{-pyridyl}}\}-3,5\text{-difluorophenyl}\}-5\{1,2\text{-oxazol\text{-}3\text{-yloxymethyl}\}-1,3\text{-oxazolidin\text{-}2\text{-one}} \)

*antibacterial*

posizolid

\( (5R)-3-[4\{(2S)-2,3\text{-dihydroxypropanoyl}\}-1,2,3,6\text{-tétrahydropyrindin\text{-}4\text{-yl}}\}-3,5\text{-difluorophényl}\}-5\{\text{(isoxazol\text{-}3\text{-yloxy})méthyl}\}oxazolidin\text{-}2\text{-one} \)

*antibactérien*

posizolid

\( (5R)-3-(4\{1\{(2S)-2,3\text{-dihidroxipropanoil}\}-1,2,3,6\text{-tetrahidro\text{-}4\text{-piridil}}\}-3,5\text{-difluorofenil}\}-5\{\text{(isoxazol\text{-}3\text{-iloxi})metil}\}oxazolidin\text{-}2\text{-ona} \)

*antibacteriano*

\[ C_{21}H_{21}F_{2}N_{3}O_{7} \]

rafabegronum

rafabegron

\( (3\{(2R)-2\{(2R)-2\{(3\text{-chlorophenyl}\)-2\text{-hydroxyethylamino}\}propyl\}-1\text{-H\text{-}indol\text{-}7\text{-yloxy}\}acetic acid} \)

*β\text{3-}adrenoreceptor agonist*

rafabégron

acide \( [3\{(2R)-2\{(2R)-2\{(3\text{-chlorophényl}\)-2\text{-hydroxyéthyl\}amino\}propyl\}-1\text{-H\text{-}indol\text{-}7\text{-yl\}oxy\}acétique} \)

*agoniste β\text{3-}adrénergique*

rafabegrón

ácido \( (3\{(2R)-2\{(2R)-2\{(3\text{-clorofenil}\)-2\text{-hidroxetilamino\}propil\}-1\text{-H\text{-}indol\text{-}7\text{-iloxi}\}acético} \)

*agonista de los receptores β\text{3-}adrenérgicos*

\[ C_{21}H_{23}ClN_{2}O_{4} \]

61
rupintrivirum

rupintrivir

(2E,4S)-4-[(2R,5S)-2-(4-fluorobenzyl)-6-methyl-5-(5-methyl-1,2-oxazol-3-carboxamido)-4-oxoheptanamido]-5-[(3S)-2-oxopyrrolidin-3-yl]pent-2-enoate

antiviral

rupintrivir

(2E,4S)-4-[(2R,5S)-2-(4-fluorobenzyl)-6-méthyl-5-[(5-méthylisoxazol-3-yl)carbonyl]amino]-4-oxoheptanoyl]amino]-5-[(3S)-2-oxopyrrolidin-3-yl]pent-2-énoate d’éthyle

antiviral

rupintrivir

(2E,4S)-4-[(2R,5S)-2-(4-fluorobencil)-6-metil-5-(5-metil-1,2-isoxazol-3-carboxamido)-4-oxoheptanamido]-5-[(3S)-2-oxipirrilodin-3-il]pent-2-enoato de etilo

antiviral

\[ C_{31}H_{39}FN_{4}O_{7} \] 223537-30-2

sorafenibum

sorafenib

4-(4-{3-[4-chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-\(N^\circ\)-methylpyridine-2-carboxamide

antineoplastic

sorafénib

4-[4-[[4-chloro-3-(trifluorométhyl)phényl]carbamoyl]amino]phénoxy]-\(N^\circ\)-méthylpyridine-2-carboxamide

antinéoplasique

sorafenib

4-(4-[3-[4-cloro-3-(trifluorometil)fenil]ureido]fenoxi)-\(N^\circ\)-metilpiridina-2-carboxamida

antineoplásico

\[ C_{21}H_{16}ClF_{3}N_{4}O_{3} \] 284461-73-0
squalaminum  
squalamine  
(24\R)-3β-[3-(4-aminobutylamino)propylamino]-7α-hydroxy-5α-cholestan-24-yl hydrogen sulfate  
antineoplastic  
squalamine  
hydrogénosulfate de (24\R)-3β-[3-[4-aminobutyl]amino]propylamino]-7α-hydroxy-5α-cholestan-24-yle  
antinéoplasique  
escualamina  
hidrógenosulfato de (24\R\S)-3β-[3-(4-aminobutilamino)propilamino]-7α-hidroxi-5α-colestan-24-ilo  
antineoplásico  
\[C_{34}H_{65}N_3O_5S\]  

\[\text{\includegraphics[width=0.5\textwidth]{squalamine结构图}}\]  


tacedinalinum  
tacedinaline  
4-acetamido-N-(2-aminophenyl)benzamide  
antineoplastic  
tácédinaline  
4-(acétylamino)-N-(2-aminophényl)benzamide  
antinéoplasique  
tacedinalina  
4-acetamido-N-(2-aminofenil)benzamida  
antineoplásico  
\[C_{15}H_{15}N_3O_2\]  

\[\text{\includegraphics[width=0.5\textwidth]{tacedinaline结构图}}\]  


telbivudinum

telbivudine

1-(2-deoxy-β-L-erythro-pentofuranosyl)-5-methylpyrimidine-2,4(1H,3H)-dione
antiviral

telbivudine

1-(2-désoxy-β-L-érythro-pentofuranosyl)-5-méthylpyrimidine-2,4(1H,3H)-dione
antiviral

telbivudina

1-(2-desoxi-β-L-eritro-pentofuranosil)-5-metilpirimidina-2,4(1H,3H)-diona
antiviral

\[ \text{C}_{10}\text{H}_{14}\text{N}_{2}\text{O}_{5} \]

3424-98-4


tolevamerum

tolevamer

poly[1-(4-sulfophenyl)ethylene]
antidiarrhoeal

tolévamer

poly[1-(4-sulfophényl)éthylène]
antidiarrhéique

tolevámero

poli[1-(4-sulfofenil)etileno]
antidiarréico

\[ (\text{C}_{8}\text{H}_{8}\text{O}_{3}\text{S})_n \]

28210-41-5
AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Proposed International Nonproprietary Names (Prop. INN): List 85
Dénominations communes internationales proposées (DCI Prop.): Liste 85
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 85
(WHO Drug Information, Vol. 15, No. 2, 2001)

p. 123 delete/supprimer/suprimase insert/insérer/inséresse

remi
tantum
remiantant
rémi
tant
remiantant
meclini
tantum
meclinertant
méclinantant
meclinertant

Proposed International Nonproprietary Names (Prop. INN): List 86
Dénominations communes internationales proposées (DCI Prop.): Liste 86
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 86
(WHO Drug Information, Vol. 16, No. 1, 2002)

p. 39 asoprisnilum
asoprisnil
asoprisnilo
replace the CAS registry number by the following:
remplacer le numéro dans le registre du CAS par:
sustitúyase le número dans le registre del CAS por:
199396-76-4

p. 51 metelimumabum
metelimumab
replace the description by the following:
immunoglobulin G4, anti-(human transforming growth factor β1) (human monoclonal CAT-192 γ4-chain), disulfide with human monoclonal CAT-192 κ-chain, dimer
remplacer la description et la formule développée par la suivante:
peptide-(24-163)-peptide
sustitúyase la descripción y la fórmula empírica por la siguiente:
péptido-(24-163)-factor de crecimiento del fibroblasto humano

p. 54 paliferminum
palifermin
palifermine
palifermina
replace the description and the graphic formula by the following:
human fibroblast growth factor-(24-163)-peptide
remplacer la description et la formule développée par la suivante:
peptide-(24-163)-facteur de croissance du fibroblaste humain
sustitúyase la descripción y la fórmula empírica por la siguiente:
péptido-(24-163)-factor de crecimiento del fibroblasto humano

SYDYMEG GDIRVRLFC
RTQWYLRIDK RGKVGTQEM KNYYNIMEIR TVAVGIVAIK
GVESEFYLAM NKEGKYAKK ECNEDCNFKE LILENYNTY
ASAKWTHNGG EMFVALNQKG IPVVRKKTKK EQKTAHFLPM
AIT
palifermin
palifermine
palifermina

replace the molecular formula by the following:
remplacer la formule brute par:
sustitúyase la fórmula molecular por:

\[ \text{C}_{724}\text{H}_{1147}\text{N}_{203}\text{O}_{206}\text{S}_{9} \]

palifermin
palifermine
palifermina

replace the CAS registry number by the following:
remplacer le numéro dans le registre du CAS par:
sustitúyase le número dans le registre du CAS por:

162394-19-6

Proposed International Nonproprietary Names (Prop. INN): List 88
Dénominations communes internationales proposées (DCI Prop.): Liste 87
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 87

p. 180 pegaptanibum
pegaptanib
pégaptanib
pegaptanib

replace the graphic formula by the following:
remplacer la formule développée par la suivante:
sustitúyase la fórmula empírica por la siguiente:

\[
\begin{align*}
x + y &= n \\
\text{H}_3\text{C} &\text{O} - \text{O} - \text{N} - \text{H} - \text{O} - \text{CH}_3 \\
\text{H}_3\text{C} &\text{O} - \text{O} - \text{N} - \text{H} - \text{O} - \text{P} - \text{RNA} \\
\end{align*}
\]

p. 182 plevitrexedum
plevitrexed
plévitrexed
plevitrexed

replace the molecular formula by the following:
remplacer la formule moléculaire par la suivante:
sustitúyase la fórmula molecular por:

\[ \text{C}_{26}\text{H}_{25}\text{FN}_{8}\text{O}_{4} \]

p. 183 soraprazanum
soraprazan
soraprazan
soraprazán

replace the action and use by the following:
remplacer la propriété et indication par la suivante:
sustitúyase la acción y el uso por los siguientes:

acid pump inhibitor
inhibiteur de la pompe à proton
inhibidor de la bomba de ácido
Due to a printing problem the following names have been published in both Proposed INN List 86 and Proposed INN List 87. Please disregard the entries published in Proposed INN List 87:

p. 171  **indiplonum**
- indiplon
- indiplon
- indiplón

p. 173  **lubazodonum**
- lubazodone
- lubazodone
- lubazodona

p. 188  **trabectedinum**
- trabectedin
- trabectédine
- trabectedina
Annex 1

PROCEDURE FOR THE SELECTION OF RECOMMENDED INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES*

The following procedure shall be followed by the World Health Organization in the selection of recommended international nonproprietary names for pharmaceutical substances, in accordance with the World Health Assembly resolution WHA3.11:

1. Proposals for recommended international nonproprietary names shall be submitted to the World Health Organization on the form provided therefor.

2. Such proposals shall be submitted by the Director-General of the World Health Organization to the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated for this purpose, for consideration in accordance with the “General principles for guidance in devising International Nonproprietary Names”, appended to this procedure. The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

3. Subsequent to the examination provided for in article 2, the Director-General of the World Health Organization shall give notice that a proposed international nonproprietary name is being considered.

   A. Such notice shall be given by publication in the *Chronicle of the World Health Organization*1 and by letter to Member States and to national pharmacopoeia commissions or other bodies designated by Member States.

   (i) Notice may also be sent to specific persons known to be concerned with a name under consideration.

   B. Such notice shall:

   (i) set forth the name under consideration;

   (ii) identify the person who submitted a proposal for naming the substance, if so requested by such person;

   (iii) identify the substance for which a name is being considered;

   (iv) set forth the time within which comments and objections will be received and the person and place to whom they should be directed;

   (v) state the authority under which the World Health Organization is acting and refer to these rules of procedure.

   C. In forwarding the notice, the Director-General of the World Health Organization shall request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the proposed name during the period it is under consideration by the World Health Organization.

4. Comments on the proposed name may be forwarded by any person to the World Health Organization within four months of the date of publication, under article 3, of the name in the *Chronicle of the World Health Organization*.1

5. A formal objection to a proposed name may be filed by any interested person within four months of the date of publication, under article 3, of the name in the *Chronicle of the World Health Organization*.1

   A. Such objection shall:

   (i) identify the person objecting;

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1 The title of this publication was changed to WHO Chronicle in January 1959. From 1987 onwards lists of INNs are published in WHO Drug Information.
(ii) state his interest in the name;

(iii) set forth the reasons for his objection to the name proposed.

6. Where there is a formal objection under article 5, the World Health Organization may either reconsider the proposed name or use its good offices to attempt to obtain withdrawal of the objection. Without prejudice to the consideration by the World Health Organization of a substitute name or names, a name shall not be selected by the World Health Organization as a recommended international nonproprietary name while there exists a formal objection thereto filed under article 5 which has not been withdrawn.

7. Where no objection has been filed under article 5, or all objections previously filed have been withdrawn, the Director-General of the World Health Organization shall give notice in accordance with subsection A of article 3 that the name has been selected by the World Health Organization as a recommended international nonproprietary name.

8. In forwarding a recommended international nonproprietary name to Member States under article 7, the Director-General of the World Health Organization shall:

A. request that it be recognized as the nonproprietary name for the substance; and

B. request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name, including prohibiting registration of the name as a trade-mark or trade-name.

Annex 2

GENERAL PRINCIPLES FOR GUIDANCE IN DEVISING INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES*

1. International Nonproprietary Names (INN) should be distinctive in sound and spelling. They should not be inconveniently long and should not be liable to confusion with names in common use.

2. The INN for a substance belonging to a group of pharmacologically related substances should, where appropriate, show this relationship. Names that are likely to convey to a patient an anatomical, physiological, pathological or therapeutic suggestion should be avoided.

These primary principles are to be implemented by using the following secondary principles:

3. In devising the INN of the first substance in a new pharmacological group, consideration should be given to the possibility of devising suitable INN for related substances, belonging to the new group.

4. In devising INN for acids, one-word names are preferred; their salts should be named without modifying the acid name, e.g. “oxacillin” and “oxacillin sodium”, “ibufenac” and “ibufenac sodium”.

5. INN for substances which are used as salts should in general apply to the active base or the active acid. Names for different salts or esters of the same active substance should differ only in respect of the name of the inactive acid or the inactive base.

For quaternary ammonium substances, the cation and anion should be named appropriately as separate components of a quaternary substance and not in the amine-salt style.

6. The use of an isolated letter or number should be avoided; hyphenated construction is also undesirable.

* In its twentieth report (WHO Technical Report Series, No. 581, 1975), the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, international nonproprietary names (INN) in the light of developments in pharmaceutical compounds in recent years. The most significant change has been the extension to the naming of synthetic chemical substances of the practice previously used for substances originating in or derived from natural products. This practice involves employing a characteristic “stem” indicative of a common property of the members of a group. The reasons for, and the implications of, the change are fully discussed.
7. To facilitate the translation and pronunciation of INN, “f” should be used instead of “ph”, “t” instead of “th”, “e” instead of “ae” or “oe”, and “i” instead of “y”; the use of the letters “h” and “k” should be avoided.

8. Provided that the names suggested are in accordance with these principles, names proposed by the person discovering or first developing and marketing a pharmaceutical preparation, or names already officially in use in any country, should receive preferential consideration.

9. Group relationship in INN (see Guiding Principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use. Where a stem is shown without any hyphens it may be used anywhere in the name.

<table>
<thead>
<tr>
<th>Latin</th>
<th>English</th>
</tr>
</thead>
<tbody>
<tr>
<td>-acum</td>
<td>-ac</td>
</tr>
<tr>
<td>-actidum</td>
<td>-actide</td>
</tr>
<tr>
<td>-adolum</td>
<td>-adol</td>
</tr>
<tr>
<td>-astum</td>
<td>-ast</td>
</tr>
<tr>
<td>-astinum</td>
<td>-astine</td>
</tr>
<tr>
<td>-azepamus</td>
<td>-azepam</td>
</tr>
<tr>
<td>-bactamum</td>
<td>-bactam</td>
</tr>
<tr>
<td>bol</td>
<td>bol</td>
</tr>
<tr>
<td>-buzonum</td>
<td>-buzone</td>
</tr>
<tr>
<td>-cain-</td>
<td>-cain-</td>
</tr>
<tr>
<td>-cainum</td>
<td>-caine</td>
</tr>
<tr>
<td>cef-</td>
<td>cef-</td>
</tr>
<tr>
<td>-cilinium</td>
<td>-cilin</td>
</tr>
<tr>
<td>-conazolum</td>
<td>-conazole</td>
</tr>
<tr>
<td>cort</td>
<td>cort</td>
</tr>
<tr>
<td>-dipinum</td>
<td>-dipine</td>
</tr>
<tr>
<td>-fibratum</td>
<td>-fibrate</td>
</tr>
<tr>
<td>gest</td>
<td>gest</td>
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<tr>
<td>gli-</td>
<td>gli-</td>
</tr>
<tr>
<td>io-</td>
<td>io-</td>
</tr>
<tr>
<td>-ium</td>
<td>-ium</td>
</tr>
<tr>
<td>-metacinum</td>
<td>-metacin</td>
</tr>
<tr>
<td>-mycinum</td>
<td>-mycin</td>
</tr>
<tr>
<td>-nidazolum</td>
<td>-nidazole</td>
</tr>
<tr>
<td>-olol</td>
<td>-olol</td>
</tr>
<tr>
<td>-oxacinum</td>
<td>-oxacin</td>
</tr>
<tr>
<td>-pridum</td>
<td>-pride</td>
</tr>
<tr>
<td>pril(at)um</td>
<td>pril(at)</td>
</tr>
<tr>
<td>-profenum</td>
<td>-profen</td>
</tr>
<tr>
<td>prost</td>
<td>prost</td>
</tr>
<tr>
<td>-relinum</td>
<td>-relin</td>
</tr>
<tr>
<td>-terolum</td>
<td>-terol</td>
</tr>
<tr>
<td>-tidinum</td>
<td>-tidine</td>
</tr>
<tr>
<td>-trexatum</td>
<td>-trexate</td>
</tr>
<tr>
<td>-verinum</td>
<td>-verine</td>
</tr>
<tr>
<td>vin-</td>
<td>vin-</td>
</tr>
</tbody>
</table>

1 A more extensive listing of stems is contained in the working document WHO/EDM/QSM 99.6 which is regularly updated and can be requested from the INN Programme, WHO, Geneva.
Annexe 1

PROCEDURE A SUIVRE EN VUE DU CHOIX DE DENOMINATIONS COMMUNES INTERNATIONALES RECOMMANDEES POUR LES SUBSTANCES PHARMACEUTIQUES*

L'Organisation mondiale de la Santé observe la procédure exposée ci-dessous pour l’attribution de dénominations communes internationales recommandées pour les substances pharmaceutiques, conformément à la résolution WHA3.11 de l'Assemblée mondiale de la Santé:

1. Les propositions de dénominations communes internationales recommandées sont soumises à l’Organisation mondiale de la Santé sur la formule prévue à cet effet.

2. Ces propositions sont soumises par le Directeur général de l’Organisation mondiale de la Santé aux experts désignés à cette fin parmi les personnalités inscrites au Tableau d’experts de la Pharmacopée internationale et des Préparations pharmaceutiques; elles sont examinées par les experts conformément aux “Directives générales pour la formation des dénominations communes internationales”, reproduites ci-après. La dénomination acceptée est la dénomination employée par la personne qui découvre ou qui, la première, fabrique et lance sur le marché une substance pharmaceutique, à moins que des raisons majeures n’obligent à s’écarter de cette règle.

3. Après l’examen prévu à l’article 2, le Directeur général de l’Organisation mondiale de la Santé notifie qu’un projet de dénomination commune internationale est à l’étude.

A. Cette notification est faite par une insertion dans la Chronique de l’Organisation mondiale de la Santé et par l’envoi d’une lettre aux États Membres et aux commissions nationales de pharmacopée ou autres organismes désignés par les États Membres.

(i) Notification peut également être faite à toute personne portant à la dénomination mise à l’étude un intérêt notoire.

B. Cette notification contient les indications suivantes:

(i) dénomination mise à l’étude;

(ii) nom de l’auteur de la proposition tendant à attribuer une dénomination à la substance, si cette personne le demande;

(iii) définition de la substance dont la dénomination est mise à l’étude;

(iv) délai pendant lequel seront reçues les observations et les objections à l’égard de cette dénomination; nom et adresse de la personne habilitée à recevoir ces observations et objections;

(v) mention des pouvoirs en vertu desquels agit l’Organisation mondiale de la Santé et référence au présent règlement.

C. En envoyant cette notification, le Directeur général de l’Organisation mondiale de la Santé demande aux États Membres de prendre les mesures nécessaires pour prévenir l’acquisition de droits de propriété sur la dénomination proposée pendant la période au cours de laquelle cette dénomination est mise à l’étude par l’Organisation mondiale de la Santé.

4. Des observations sur la dénomination proposée peuvent être adressées à l’Organisation mondiale de la Santé par toute personne, dans les quatre mois qui suivent la date de publication de la dénomination dans la Chronique de l’Organisation mondiale de la Santé (voir l’article 3).


1 Depuis janvier 1959, cette publication porte le titre de Chronique OMS. A partir de 1987, les listes des DCIs sont publiées dans les Informations pharmaceutiques OMS.
5. Toute personne intéressée peut formuler une objection formelle contre la dénomination proposée dans les quatre mois qui suivent la date de publication de la dénomination dans la *Chronique de l’Organisation mondiale de la Santé* (voir l’article 3).

   A. Cette objection doit s’accompagner des indications suivantes:

   i) nom de l’auteur de l’objection;

   ii) intérêt qu’il porte à la dénomination en cause;

   iii) raisons motivant l’objection contre la dénomination proposée.

6. Lorsqu’une objection formelle est formulée en vertu de l’article 5, l’Organisation mondiale de la Santé peut soit soumettre la dénomination proposée à un nouvel examen, soit intervenir pour tenter d’obtenir le retrait de l’objection. Sans préjudice de l’examen par elle d’une ou de plusieurs appellations de remplacement, l’Organisation mondiale de la Santé n’adopte pas d’appellation comme dénomination commune internationale recommandée tant qu’une objection formelle présentée conformément à l’article 5 n’est pas levée.

7. Lorsqu’il n’est formulé aucune objection en vertu de l’article 5 ou que toutes les objections présentées ont été levées, le Directeur général de l’Organisation mondiale de la Santé fait une notification conformément aux dispositions de la sous-section A de l’article 3, en indiquant que la dénomination a été choisie par l’Organisation mondiale de la Santé en tant que dénomination commune internationale recommandée.

8. En communiquant aux États Membres, conformément à l’article 7, une dénomination commune internationale recommandée, le Directeur général de l’Organisation mondiale de la Santé:

   A. demande que cette dénomination soit reconnue comme dénomination commune de la substance considérée, et

   B. demande aux États Membres de prendre les mesures nécessaires pour prévenir l’acquisition de droits de propriété sur cette dénomination, notamment en interdisant le dépôt de cette dénomination comme marque ou appellation commerciale.

**Annexe 2**

**DIRECTIVES GÉNÉRALES POUR LA FORMATION DE DÉNOMINATIONS COMMUNES INTERNATIONALES APPLICABLES AUX SUBSTANCES PHARMACEUTIQUES***

1. Les dénominations communes internationales (DCI) devront se distinguer les unes des autres par leur consonance et leur orthographe. Elles ne devront pas être d’une longueur excessive, ni prêter à confusion avec des appellations déjà couramment employées.

2. La DCI de chaque substance devra, si possible, indiquer sa parenté pharmacologique. Les dénominations sus-ceptibles d’évoquer pour les malades des considérations anatomiques, physiologiques, pathologiques ou thérapeutiques devront être évitées dans la mesure du possible.

*Outre ces deux principes fondamentaux, on respectera les principes secondaires suivants:*

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*Dans son vingtième rapport (Série de Rapports techniques de l’OMS, No. 581, 1975), le Comité OMS d’experts des Dénominations communes pour les Substances pharmaceutiques a examiné les directives générales pour la formation des dénominations communes internationales et la procédure à suivre en vue de leur choix, compte tenu de l’évolution du secteur pharmaceutique au cours des dernières années. La modification la plus importante a été l’extension aux substances de synthèse de la pratique normalement suivie pour désigner les substances tirées ou dérivées de produits naturels. Cette pratique consiste à employer des syllabes communes ou groupes de syllabes communes (segments clés) qui sont caractéristiques et indiquent une propriété commune aux membres du groupe des substances pour lequel ces segments clés ont été retenus. Les raisons et les conséquences de cette modification ont fait l’objet de discussions approfondies.*
3. Lorsqu’on formera la DCI de la première substance d’un nouveau groupe pharmacologique, on tiendra compte de la possibilité de former ultérieurement d’autres DCI appropriées pour les substances apparentées du même groupe.

4. Pour former des DCI des acides, on utilisera de préférence un seul mot. Leurs sels devront être désignés par un terme qui ne modifie pas le nom de l’acide d’origine: par exemple “oxacilline” et “oxacilline sodique”, “ibufénac” et “ibufénac sodique”.

5. Les DCI pour les substances utilisées sous forme de sels devront en général s’appliquer à la base active (ou à l’acide actif). Les dénominations pour différents sels ou esters d’une même substance active ne différeront que par le nom de l’acide inactif (ou de la base inactive).

En ce qui concerne les substances à base d’ammonium quaternaire, la dénomination s’appliquera de façon appropriée au cation et à l’anion en tant qu’éléments distincts d’une substance quaternaire. On évitera de choisir une désignation évoquant un sel aminé.

6. On évitera d’ajouter une lettre ou un chiffre isolé; en outre, on renoncera de préférence au trait d’union.

7. Pour simplifier la traduction et la prononciation des DCI, la lettre “f” sera utilisée à la place de “ph”, “t” à la place de “th”, “e” à la place de “ae” ou “oe” et “i” à la place de “y”; l’usage des lettres “h” et “k” sera aussi évité.

8. On retiendra de préférence, pour autant qu’elles respectent les principes énoncés ici, les dénominations proposées par les personnes qui ont découvert ou qui, les premières, ont fabriqué et lancé sur le marché les préparations pharmaceutiques considérées, ou les dénominations déjà officiellement adoptées par un pays.

9. La parenté entre substances d’un même groupe (voir Directive générale 2) sera si possible indiquée dans les DCI par l’emploi de segments clés communs. La liste ci-après contient des exemples de segments clés pour des groupes de substances, surtout pour des groupes récents. Il y a beaucoup d’autres segments clés en utilisation active.1 Les segments clés indiqués sans trait d’union pourront être insérés n’importe où dans une dénomination.

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<th>Latin</th>
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1 Une liste plus complète de segments clés est contenue dans le document de travail WHO/EDM/QSM 99.6 qui est régulièrement mis à jour et qui peut être demandé auprès du Programme des DCI, OMS, Genève.
La Organización Mundial de la Salud seguirá el procedimiento que se expone a continuación para la selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas, de conformidad con lo dispuesto en la resolución WHA3.11 de la Asamblea Mundial de la Salud:

1. Las propuestas de denominaciones comunes internacionales recomendadas se presentarán a la Organización Mundial de la Salud en los formularios que se proporcionen a estos efectos.

2. Estas propuestas serán sometidas por el Director General de la Organización Mundial de la Salud a los Miembros del Cuadro de Expertos de la Farmacopea Internacional y las Preparaciones Farmacéuticas encargados de su estudio, para que las examinen de conformidad con los “Principios Generales de Orientación para formar Denominaciones Comunes Internacionales para Sustancias Farmacéuticas”, anexos a este Procedimiento. A menos que haya poderosas razones en contra, la denominación aceptada será la empleada por la persona que haya descubierto, fabricado o puesto a la venta por primera vez una sustancia farmacéutica.

3. Una vez terminado el estudio a que se refiere el artículo 2, el Director General de la Organización Mundial de la Salud notificará que está en estudio un proyecto de denominación internacional.

A. Esta notificación se hará mediante una publicación en la Crónica de la Organización Mundial de la Salud\(^{1}\) y el envío de una carta a los Estados Miembros y a las comisiones nacionales de las farmacopeas u otros organismos designados por los Estados Miembros.

(i) La notificación puede enviarse también a las personas que tengan un interés especial en una denominación objeto de estudio.

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\(^{2}\) Denominada Crónica de la OMS desde enero de 1959. A partir de 1987, las listas de DCI se publican en Información Farmacéutica OMS.
B. En estas notificaciones se incluyen los siguientes datos:

(i) denominación sometida a estudio;

(ii) nombre de la persona que ha presentado la propuesta de denominación de la sustancia si lo pide esta persona;

(iii) definición de la sustancia cuya denominación está en estudio;

(iv) plazo fijado para recibir observaciones y objeciones, así como nombre y dirección de la persona a quien deban dirigirse, y

(v) mención de los poderes conferidos para el caso a la Organización Mundial de la Salud y referencia al presente procedimiento.

C. Al enviar esta notificación, el Director General de la Organización Mundial de la Salud solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de propiedad sobre la denominación propuesta, durante el periodo en que la Organización Mundial de la Salud tenga en estudio esta denominación.

4. Toda persona puede formular a la Organización Mundial de la Salud observaciones sobre la denominación propuesta, dentro de los cuatro meses siguientes a su publicación en la Crónica de la Organización Mundial de la Salud, conforme a lo dispuesto en el artículo 3.

5. Toda persona interesada puede presentar una objeción formal contra la denominación propuesta, dentro de los cuatro meses siguientes a su publicación en la Crónica de la Organización Mundial de la Salud, conforme a lo dispuesto en el artículo 3.

A. Esta objeción deberá acompañarse de los siguientes datos:

i) nombre de la persona que formula la objeción;

ii) causas que motivan su interés por la denominación, y

iii) causas que motivan su objeción a la denominación propuesta.

6. Cuando se haya presentado una objeción formal en la forma prevista en el artículo 5, la Organización Mundial de la Salud puede someter a nuevo estudio la denominación propuesta, o bien utilizar sus buenos oficios para lograr que se retire la objeción. Sin perjuicio de que la Organización Mundial de la Salud estudie una o varias denominaciones en sustitución de la primitiva, ninguna denominación podrá ser seleccionada por la Organización Mundial de la Salud como denominación común internacional recomendada en tanto que exista una objeción formal, presentada como previene el artículo 5, que no haya sido retirada.

7. Cuando no se haya formulado ninguna objeción en la forma prevista en el artículo 5, o cuando todas las objeciones presentadas hayan sido retiradas, el Director de la Organización Mundial de la Salud notificará, conforme a lo dispuesto en el párrafo A del artículo 3, que la denominación ha sido seleccionada por la Organización Mundial de la Salud como denominación común internacional recomendada.

8. Al comunicar a los Estados Miembros una denominación común internacional conforme a lo previsto en el artículo 7, el Director General de la Organización Mundial de la Salud:

A. solicitará que esta denominación sea reconocida como denominación común para la sustancia de que se trate, y

B. solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de propiedad sobre la denominación, incluso la prohibición de registrarla como marca de fábrica o como nombre comercial.
Anexo 2

PRINCIPIOS GENERALES DE ORIENTACIÓN PARA FORMAR DENOMINACIONES COMUNES INTERNACIONALES PARA SUSTANCIAS FARMACEUTICAS*

1. Las Denominaciones Comunes Internacionales (DCI) deberán diferenciarse tanto fonéticamente como ortográficamente. No deberán ser incómodamente largas, ni dar lugar a confusión con denominaciones de uso común.

2. La DCI de una sustancia que pertenezca a un grupo de sustancias farmacológicamente emparentadas deberá mostrar apropiadamente este parentesco. Deberán evitarse los nombres que puedan inducir fácilmente en el paciente sugestiones anatómicas, fisiológicas, patológicas o terapéuticas.

Estos principios primarios deberán ser tenidos en cuenta al aplicar los siguientes principios secundarios:

3. Al idear la DCI de la primera sustancia de un nuevo grupo farmacológico, deberá tenerse en cuenta la posibilidad de formar DCI convenientes para las sustancias emparentadas que vengan a incrementar el nuevo grupo.

4. Al idear DCI para ácidos, se preferirán las de una sola palabra; sus sales deberán denominarse sin modificar el nombre de ácido; p. ej., “oxacilina” y “oxacilina sódica”, “ibufenaco” e “ibufenaco sódico”.

5. Las DCI para las sustancias que se usan en forma de sal, deberán en general aplicarse a la base activa o, respectivamente, al ácido activo. Las denominaciones para diferentes sales o ésteres de la misma sustancia activa solamente deberán diferir en el nombre de ácido o de la base inactivos.

En los compuestos de amonio cuaternario, el catión y el anión deberán denominarse adecuadamente por separado, como componentes independientes de una sustancia cuaternaria y no como sales de una amina.

6. Deberá evitarse el empleo de una letra o un número aislados; también es indeseable el empleo de guiones.

7. Para facilitar la traducción y la pronunciación se emplearán de preferencia las letras “f” en lugar de “ph”, “t” en lugar de “th”, “e” en lugar de “ae” u “oe” e “i” en lugar de “y”; se deberá evitar el empleo de las letras “h” y “k”.

8. Siempre que las denominaciones que se sugieran estén de acuerdo con estos principios, recibiran una consideración preferente las denominaciones propuestas por la persona que haya descubierto la sustancia, o la que primeramente fabrique o ponga a la venta la sustancia farmacéutica, así como las denominaciones oficialmente adoptadas en cualquier país.

9. En las DCI, la relación de grupo o parentesco (véanse los Principios Generales de Orientación, apartado 2) se indicará en lo posible utilizando una partícula común. En la lista siguiente se dan algunos ejemplos de estas partículas en relación con diversos grupos de sustancias, en particular los de nuevo cuño. Hay otras muchas partículas comunes en uso.1 Cuando la partícula no lleva ningún guión, cabe utilizarla en cualquier parte de la denominación.

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* En su 20° informe (OMS, Serie de Informes Técnicos, No. 581, 1975) el Comité de Expertos de la OMS en Denominaciones Comunes para Sustancias Farmacéuticas examina los principios generales de orientación para formar denominaciones comunes internacionales (DCI) y el procedimiento de selección de las mismas, teniendo en cuenta las novedades registradas en los últimos años en materia de preparaciones farmacéuticas. Entre las modificaciones, la más importante ha sido la extensión a las sustancias químicas sintéticas de la práctica reservada anteriormente para designar sustancias originarias o derivadas de productos naturales. Esta práctica consiste en emplear una partícula característica que indique una propiedad común a los miembros de un determinado grupo de sustancias. En el informe se examinan a fondo las razones de esta modificación y sus consecuencias.

1 El documento de trabajo WHO/EDM/QSM 99.6, que se pone al día regularmente, contiene una lista más extensa de partículas comunes. Las personas que deseen recibirlo deberán solicitar su envío al Programa DCI, OMS, Ginebra (Suiza).
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<td>-ast antiasmáticos y antialérgicos que no actúan principalmente como antihistamínicos</td>
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<td>-azepam sustancias del grupo del diazepam</td>
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<td>-bactamum</td>
<td>-bactam inhibidores de β-lactamasas</td>
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<td>bol esteroides anabólitantes</td>
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<td>-cain- antifibrilantes con actividad anestésica local</td>
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<td>cef- antibióticos derivados del ácido cefalosporánico</td>
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<td>-metacina antiinflamatorios del grupo de la indometacina</td>
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<td>-micina antibióticos, producidos por cepas de Streptomyces</td>
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