WHO Drug Information provides an overview of topics relating to drug development and regulation that are of current relevance and importance, and will include the lists of proposed and recommended International Nonproprietary Names for Pharmaceutical Substances (INN). Its contents reflect, but do not present, WHO policies and activities and they embrace socioeconomic as well as technical matters.

The objective is to bring issues that are of primary concern to drug regulators and pharmaceutical manufacturers to the attention of a wide audience of health professionals and policy-makers concerned with the rational use of drugs. In effect, the journal seeks to relate regulatory activity to therapeutic practice. It also aims to provide an open forum for debate. Invited contributions will portray a variety of viewpoints on matters of general policy with the aim of stimulating discussion not only in these columns but wherever relevant decisions on this subject have to be taken.

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Further proposals on the WHO Certification Scheme

Throughout the past year the World Health Organization has continued to consult both national regulatory authorities and organizations representative of the pharmaceutical industry on the implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce. The prime objective has been to consider how the existing certification procedure might be effectively modified to frustrate fraudulent use of the Scheme and to stem illicit trade in falsely-labelled, spurious, counterfeited and substandard pharmaceutical products.

The provisional guidelines and certificates reproduced below — which will need to be adopted by the World Health Assembly before they can become formally operative — were endorsed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations during its meeting in December 1990 without prejudice to any changes that may be considered necessary in the course of further consultation.

Comments are invited from any interested party, particularly on the practicability of the proposed procedures and on the question of confidentiality of information. There is wide recognition, none the less, that the current situation calls for the greatest possible degree of transparency in the marketing of pharmaceutical products. Communications, which should be addressed to the Division of Drug Management and Policies, World Health Organization, 1211 Geneva 27, Switzerland, should arrive before the end of June 1991. After this date, it is anticipated that several importing and exporting countries will collaborate in a feasibility study of the proposals.

PROVISIONAL GUIDELINES FOR USE

1. Provisions and objectives

1.1 A comprehensive system of quality assurance must be founded on a reliable system of licensing and independent analysis of the finished product, as well as upon assurance obtained through independent inspection that all manufacturing operations are carried out in conformity with accepted norms, referred to as "good manufacturing practices" (GMP).

1.2 In 1969, the Twenty-eighth World Health Assembly endorsed Requirements for Good Practices in the Manufacture and Quality Control of Drugs (referred to henceforth as "GMP as recommended by WHO"). These comprize internationally recognized and respected standards that all Member States are urged to adopt and to apply.

1.3 These standards provide the basis for the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce (referred to henceforth as "the Scheme") which was promulgated in the same resolution. This is an administrative instrument that requires each participating Member State, upon application by a commercially interested party, to attest to the competent authority of another participating Member State whether:

- a specific product is authorized to be placed on the market within its jurisdiction;
- the plant in which it is produced is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP as recommended by WHO; and

---

1 Throughout this document "licensing" refers to any statutory system of approval required at national level as a precondition for placing a pharmaceutical product on the market. 2 Resolution WHA22.50, 1969. 3 WHO Official Records, No. 176, Annex 12, part one. 4 WHO Official Records, No. 176, Annex 12, part two.
• all submitted product information, including labelling, is currently authorized in the certifying country.

1.4 The Scheme, as subsequently amended in 1975 and 1988, is applicable to finished dosage forms of pharmaceutical products:

• intended for administration to human beings, and

• intended for administration to food-producing animals.

1.5 Provision for certification of starting materials is also included within the scope of the Scheme. This will be the subject of separate guidelines and certificates.

2. Eligibility for participation

2.1 Any Member State intending to participate in the Scheme may do so by notifying the Director-General of the World Health Organization, in writing, of:

• its willingness to participate in the Scheme;

• any significant reservations it intends to observe relating to this participation; and

• the name and address of its national drug regulatory authority or other competent authority.

2.2 These notifications are subsequently announced in the monthly WHO Pharmaceutical Newsletter. An updated consolidated list will be published annually in the Newsletter and will be available to governments at other times from: the Division of Drug Management and Policies, WHO, 1211 Geneva 27, Switzerland.

2.3 A Member State may opt to participate solely to control the import of pharmaceutical products and substances. This intention should be stated explicitly in its notification to the World Health Organization.

2.4 A Member State intending to use the Scheme to support the export of pharmaceutical products should first satisfy itself that it possesses:

• an effective national licensing system, not only for pharmaceutical products, but also for the responsible manufacturers and distributors;

• GMP requirements, consonant with those recommended by WHO, to which all manufacturers of finished pharmaceutical products are required to conform;

• effective controls to monitor the quality of pharmaceutical products registered or manufactured within its country, including access to an independent quality control laboratory;

• a national pharmaceuticals inspectorate, operating as an arm of the national drug regulatory authority, that possesses the technical competence, experience and resources to assess whether GMP and other controls are being effectively implemented, and with the legal power to conduct appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples;

• administrative capacity to issue the required certificates, to institute inquiries in the case of complaint, and to notify expeditiously both WHO and the competent authority in any Member State known to have imported a specific product that is subsequently associated with a potentially serious quality defect or other hazard.

2.5 Each Member State assumes the responsibility to determine, through a process of self-evaluation, whether it satisfies these prerequisites. The Scheme contains no provision, under any circumstance, for external inspection or assessment, either of a competent national authority or of a manufacturing facility.

3. Requesting a certificate

3.1 Three documents can be requested within the scope of the scheme:

Certificate of a Pharmaceutical Product

Statement of Licensing Status of Pharmaceutical Product(s)

Batch Certificate of a Pharmaceutical Product.

5 Resolution WHA 28.65, 1975. 6 WHO Official Records, No. 226, 1975, p. 88. 7 Resolution WHA 41.18, 1988. 8 Document WHA41/1988/REC/1, p. 53. 9 The format of the attached documents will ultimately need to be adopted by the World Health Assembly. These recommendations are offered without prejudice to any changes that may be considered necessary in the course of consultations with governments and other interested parties.
3.2 Proposed formats for these documents are provided in Annexes 1 to 3 of these guidelines. All participating countries are henceforth urged to adopt these formats to facilitate interpretation of certified information.

3.3 A list of addresses of competent national authorities participating in the Scheme, together with details of any reservations they have declared regarding their participation in the Scheme, may be obtained from WHO as indicated in section 2.2.

3.4 The competent authority in each country participating in the Scheme should issue guidelines to all agents responsible for importing pharmaceutical and veterinary products that operate under its jurisdiction, including those responsible for public sector purchases, to explain the contribution of certification to the drug regulatory process and the circumstances in which each of the three types of documents will be required.

3.5 The Certificate of a Pharmaceutical Product (Annex 1) is intended for use by the competent authority within an importing country in two situations:

- when the product in question is under consideration for a product licence that will authorize its importation and sale;

- when administrative action is required to renew, extend, vary or review the above licence.

3.6 All requests for certificates should be channelled through the agent in the importing country and the product licence holder or other commercially-interested party in the exporting country ("the applicant"). The following information should be submitted for each product:

- Brand name.
- Generic name (INN where such exists).
- Labelling on retail and wholesale containers.
- Retail packaging (for non-prescription products only).
- Package insert.
- Name and address of manufacturing facility.
- Formulation (when no product licence exists or when the formulation differs from that of the licensed product).

3.7 The certificate is a confidential document. As such, it can be issued by the competent authority in the exporting country ("the certifying authority") only with the permission of the applicant and, if different, of the product licence holder.

3.8 The certificate is intended to form part of a product licence application. Once prepared, it is transmitted to the requesting authority through the applicant and, when applicable, the agent in the importing country.

3.9 When any doubt arises about the status or validity of a certificate, the competent authority in the importing country should request a copy directly from the certifying authority, as provided for under section 4.9 of these guidelines.

3.10 In the absence of any specific agreement, each certificate will be prepared exclusively in the working language(s) of the certifying authority. The applicant will be responsible for providing any notarized translation that may be required by the requesting authority.

3.11 Since the preparation of certificates imposes a significant administrative load on certifying authorities, the service may need to be financed by charges levied upon applicants.

3.12 Supplementary attestations are obtainable only at the discretion of the certifying authority and with the permission of the applicant. The certifying authority is under no obligation to supply additional information. Requests for supplementary information should consequently be referred to the applicant, and only in exceptional circumstances to the certifying authority.

3.13 Statement of Licensing Status (Annex 2). This attests only whether or not a specified product, or products, are licensed for use in the exporting country. It is intended for use by importing agents when considering bids made in response to an international tender, in which case it should be requested by the agent as a condition of bidding. It is intended only to facilitate the screening and preparation of information. The importation of any product that is provisionally selected through this procedure should be determined on the basis of a Certificate of a Pharmaceutical Product.

3.14 Batch certificate (Annex 3). Certification of individual batches of a pharmaceutical product is normally undertaken by the manufacturer and only exceptionally, as in the case of vaccines and some other biological products, by the competent authority of the exporting country. Batch certificates are intended to accompany and provide an attestation on the quality and expiry date of a specific batch or consignment of a product that has already been licensed in the importing country. In most circumstances these certificates are issued to the importing agent (i.e. the product licence holder in the importing country), but they must be made available at the request of — or in the
course of any inspection made on behalf of — the com-
petent national authority.

4. Issuing a certificate

4.1 The certifying authority holds responsibility for
assuring the authenticity of the certified data. Certifi-
cates should not bear the emblem of the World Health
Organization, but a statement should always be in-
cluded to confirm whether or not the document is is-
issued in the format recommended by WHO.

4.2 When the applicant is the manufacturer of the fin-
ished dosage form, the certifying authority should sat-
isfy itself, before attesting compliance with GMP, that
the applicant:

• applies identical standards to the production of all
batches of pharmaceutical products manufactured
within the facility, including those destined ex-
clusively for export.

• consents to relevant inspection reports being re-
leased, in confidence, to the competent authority in
the country of import, should the latter so require.

4.3 When the applicant is not the manufacturer of the
finished dosage form, the certifying authority should
similarly satisfy itself — insofar that it has authority to
inspect the records and relevant activities of the appli-
cant — that it has the applicant's consent to release
relevant reports on the same basis as described in
section 4.2 above.

4.4 GMP as recommended by WHO assigns to the
manufacturer of the finished dosage form responsibil-
ity for assuring the quality of starting materials. National
regulations may require that suppliers of starting ma-
terials be identified in the product licence, but the
competent authority may have no power to inspect
them.

4.5 Notwithstanding this situation, a certifying author-
ity may agree, on a discretionary and voluntary basis,
and at the request of a manufacturer, to undertake an
inspection of a manufacturer of starting materials to
satisfy specific requirements of a requesting author-
ity. Alternatively, the certifying authority may be able
to attest that the manufacturer is an established sup-
plier of the substance in question to manufacturers of
finished dosage forms licensed for marketing under
its jurisdiction.

4.6 Whenever a product is purchased through a bro-
er or another intermediary, or when more than one
set of premises has been involved in the manufacture
and packaging of a product, the certifying authority
should consider whether it has received sufficient in-
formation to satisfy itself that those aspects of the
manufacture of the product for which the applicant is
not directly responsible have been undertaken in com-
pliance with GMP as recommended by WHO.

4.7 The certifying authority should stamp and date all
copies of information and labelling submitted to it in
support of an application for a certificate. Every effort
should be made to ensure that certificates are conso-
nant with the version of the product licence operative
on the date of issue. Where this is not feasible in every
particular, the information must be established as being
accurate with regard to indications for use, dosage in-
structions, precautions and contraindications.

4.8 Any attachment to a certificate submitted by the
applicant, such as price lists of products for which bids
are offered, should be clearly identified as not com-
prising part of the attestation made by the certifying
authority.

4.9 To avert potential abuse of the Scheme, to frus-
trate attempts at falsification, to render routine authen-
tication of certificates by an independent authority
superfluous and to enable the certifying authority to
maintain comprehensive records of countries to which
specific products have been exported, each certificate
should identify the importing country authority and be
stamped on each page with the official seal of the cer-
tifying authority. An identical copy, clearly marked as
duplicate, should be forwarded by the certifying au-
thority on demand directly to the importing country
authority.

5. Notifying and investigating
a quality defect

5.1 Each certifying authority undertakes to institute en-
quiries into any quality defect reported in a product ex-
ported in accordance with the provisions of the
Scheme, on the understanding that:

• the complaint is transmitted, together with the rele-
vant facts, through the competent authority in the
importing country;

• the complaint is considered to be of a serious na-
ture by the latter authority; and

• the defect, if it appeared after delivery of the prod-
uct into the importing country, is not attributable to
local conditions.
5.2 In the case of obvious doubt, a participating national authority may request the World Health Organization to assist in identifying an independent collaborating centre to carry out tests for the purposes of quality control.

5.3 Each certifying authority undertakes to inform the World Health Organization and, as far as is possible, all competent national authorities, of any serious hazard newly associated with a product exported under the provisions of the Scheme and of any fraudulent representation made in respect of a certified product. On receipt of such notification, WHO will transmit the message immediately to the competent national authorities in each Member State.

5.4 The World Health Organization stands prepared to offer advice should difficulty arise in implementing any aspect of the Scheme or in resolving a complaint, but it cannot be a party to any resulting litigation or arbitration.
ANNEX 1

General Instructions

1. Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the scheme.
2. Forms should be completed using a typewriter to assure legibility.
3. A cross should be placed in squares as appropriate to indicate which options apply.
4. Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory Notes

1. This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.
2. Use, whenever possible, international nonproprietary names (INNs) or national nonproprietary names.
3. When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is entered into the product licence.
4. Specify whether the person responsible for placing the product on the market:
   (a) manufactures the active ingredients and the finished dosage form;
   (b) manufactures the finished dosage form;
   (c) repackages and/or relabels a finished dosage form manufactured by an independent company; or
   (d) is involved in none of the above.
5. Indicate, when applicable, if the licence is provisional, pending technical review.
6. This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.
7. In this circumstance, permission for issuance of the certificate is required from the product licence holder.
8. Please indicate the reason that the applicant has provided for not requesting registration, e.g.:
   • has the product been developed exclusively for the treatment of conditions — particularly tropical diseases — not endemic in the country of export?
   • has the product been reformulated with a view to improving its stability under tropical conditions?
   • has the product been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import?
   • has the product been reformulated to meet a different maximum dosage limit for an active ingredient?
9. The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those adopted by the Twenty-eighth World Health Assembly in its resolution WHA28.65 (see WHO Official Records, No. 226, 1975, Annex 12, Part 1). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization and are published in the WHO Technical Report Series.
10. This section is to be completed when the product licence holder or applicant conforms to status (c) or (d) as described in note 4 above. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.
Certificate of a Pharmaceutical Product

Proprietary name (if applicable) and dosage form:       Active ingredient(s) and amount(s) per unit dose:

1. Is this product licensed to be placed on the market for use in the exporting country? If yes, complete box A; if no, complete box B

A

Product licence holder:
Status of licence holder: a □ b □ c □ d □
Number of product licence and date of issue:
Is an approved technical summary appended? yes □ no □
Is the attached product information complete and consonant with the licence? yes □ no □ not provided

B

Applicant for certificate:
Status of applicant: a □ b □ c □ d □
Why is authorization lacking?:
not □ not □ under □ refused □
required □ requested □ consideration
Remarks:

2. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? yes □ no □

Date of most recent inspection:
Has the manufacture of this type of dosage form been inspected? yes □ no □
Do the facilities and operations conform to GMP as recommended by the World Health Organization? yes □ no □

3. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product undertaken by another party? yes □ no □ If no, explain:

Address of certifying authority: Name of authorized person:
Signature: Stamp and date:

Telephone/fax numbers:

This certificate conforms to the format recommended by the World Health Organization.

(Explanatory Notes and General Instructions are given above)
ANNEX 2

General Instructions

1. Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the scheme.

2. Forms should be completed using a typewriter to assure legibility.

3. Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory Notes

1 This statement is intended for use by importing agents who are required to screen bids made in response to an international tender and they should be requested by the agent as a condition of bidding. The certificate indicates that the listed products are authorized to be placed on the market for use in the exporting country. A Certificate of a Pharmaceutical Product in the format recommended by WHO will be provided, at the request of the applicant and, if different, the product licence holder, for each of the listed products.

2 Use, whenever possible, international nonproprietary names (INNs) or national nonproprietary names.

3 If no product licence has been granted, enter "not required", "not requested", "under consideration" or "refused" as appropriate.
Statement of Licensing Status of Pharmaceutical Product(s)

This statement indicates only whether or not the following products are licensed to be placed on the market for use in the exporting country.

Applicant (name/address):

<table>
<thead>
<tr>
<th>Proprietary name (if applicable)</th>
<th>Dosage form:</th>
<th>Active ingredient(s) and amount(s) per unit dose:</th>
<th>Product licence No. &amp; Date of Issue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The certifying authority undertakes to provide, at the request of the product licence holder, a separate and complete certificate in the format recommended by WHO, for each of the products listed above.

Address of certifying authority:
Telephone/fax numbers:

Name of authorized person:
Signature:
Stamp and date:

This certificate conforms to the format recommended by the World Health Organization
(Explanatory Notes and General Instructions are given above)
ANNEX 3

General Instructions

1. Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the scheme.

2. Forms should be completed using a typewriter to assure legibility.

3. A cross should be placed in squares as appropriate to indicate which options apply.

4. Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory Notes for Batch Certificate

Certification of individual batches of a pharmaceutical product is only undertaken exceptionally by the competent authority of the exporting country. Even then, it is rarely applied other than to vaccines and biologicals. For other products, the responsibility for any requirement to provide batch certificates rests with the product licence holder in the exporting country. The responsibility to forward certificates to the competent authority in the importing country is most conveniently assigned to the importing agent.

1 Any inquiries or complaints regarding a batch certificate should always be addressed to the competent authority in the exporting country. A copy should be sent to the product licence holder.

2 Use, whenever possible, international nonproprietary names (INNs) or national nonproprietary names.

3 All items within this box refer to the product licence or the Certificate of a Pharmaceutical Product issued in the exporting country.

4 This refers to the Certificate of a Pharmaceutical Product as recommended by the World Health Organization.

5 Indicate any special storage conditions recommended for the product as supplied.

6 Identify and explain any discrepancies from specifications.

7 If yes, provide details of the method and results. If no, explain.
Batch Certificate of a Pharmaceutical Product

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**Quality analysis**

Do pharmacopoeial specifications apply? [ ] yes [ ] no [ ] If yes, specify the pharmacopoeia. If no, append the specification.

Does the batch comply in all particulars with the above specifications? [ ] yes [ ] no [ ] Append certificate of analysis.

Have batch dissolution tests been undertaken? [ ] yes [ ] no [ ] Remarks:

It is hereby certified that the above declarations are correct and that results of the analyses and assays on which they are based will be provided on request to the competent authorities in both the importing and exporting countries.

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This certificate conforms to the format recommended by the World Health Organization

*(Explanatory Notes and General Instructions are given above)*
Reports on Individual Drugs

H. influenzae conjugate vaccines: setbacks and successes

It is estimated that about one in every 2,000 children in the United States contracts Haemophilus influenzae type b meningitis before the age of 5 (1). However, among native Amerindians living within reservations, the attack rate is higher and the age of peak incidence is lower. Indeed, most cases occur in children under 1 year of age (2, 3). The difference, which is unlikely to reflect genetic factors, has been attributed to adverse social conditions and particularly to greater crowding, lower nutritional status and a higher prevalence of infection (4-6).

It was anticipated that the first of a new generation of polysaccharide-protein conjugate vaccines — a capsular H. influenzae type b polysaccharide conjugated to diphtheria toxoid — would be sufficiently immunogenic to protect children at greatest risk of serious systemic infection. However, whereas it has proved to be substantially, but incompletely protective in Finnish children living in privileged social conditions and particularly in those under 1 year of age (5), it has failed to confer protection against systemic Haemophilus influenzae type b infections in native Alaskan children under 1 year of age (6).

This setback is disappointing, but it may well be short-lived. The immunogenicity of the same capsular polysaccharide is reported to be enhanced when conjugated with other proteins, including tetanus toxoid and outer-membrane protein from Neisseria meningitidis (7-9). It seems that results of trials shortly to be published will confirm that these second generation products reliably induce protective titres of antibodies in all infants throughout the first year of life (4).

References


Treatment of hyperlipidaemia in high-risk patients

Some of the problematic aspects of using lipid-lowering drugs on a community scale in the primary prophylaxis of coronary heart disease were discussed in the last issue of this journal. This did not contest the existence of a fundamental association between high serum cholesterol levels and the process of atherosclerosis. It has even been suggested that other risk factors, including smoking and hypertension may become fully operative only
when some threshold degree of hypercholesterolaemia has developed (1). Re-examination of pre-existing data indicates that, for each 1 per cent increase in serum cholesterol level, the risk of coronary heart disease increases by some 3 per cent (2). Moreover, atherosclerosis is now recognized to be a process that starts in childhood or early adult life (3, 4).

Screening of blood lipids in these age groups is probably best limited to children from high-risk families (5), but there is a need for dietary adjustment through education in every community where fat provides a high proportion of total energy requirements. Experience in North America, where the National Cholesterol Education Program was introduced in 1986 (6), has shown that health warnings, vigorously promoted, can change community life-styles. Total fat intake — and the proportion of saturated fats in the average diet — has fallen appreciably there since the 1960s (7). This trend has been accompanied by a dramatic decrease in cigarette consumption, and by more active intervention to control mild hypertension and diabetes.

These approaches, however, provide incomplete protection to patients who are genetically predisposed to develop atherosclerosis (8) — possibly as many as 1 in every 500 persons in North America (9) — and to patients with established coronary heart disease. It is important to assess what can be achieved by intensive use of lipid-lowering drugs in these groups, and each of 5 recently-published controlled studies in which atherosclerotic lesions were monitored by coronary angiography (10-14) concludes not only that their progression can be demonstrably slowed by drug therapy but that, in some instances, regression can be induced. Different regimens based, notably, upon colestipol, lovastatin and nicotinic acid, often employed in combination, were compared. Each greatly reduced serum levels of atherogenic low-density lipoprotein cholesterol, while those of the "protective" high-density lipoprotein cholesterol were increased in variable degree.

Only in one study — in which particularly intensive hypolipidaemic regimens were used involving diet together with colestipol in combination with either lovastatin or nicotinic acid — has evidence been presented to suggest these changes have clinical implications. In this instance, treatment was correlated with a reduction in adverse cardiovascular events, defined as fatal or non-fatal myocardial infarction, and bypass surgery undertaken to alleviate worsening symptoms (12). Lovastatin and nicotinic acid have also been identified in an independent review of published studies as the most cost-effective agents in reducing low density lipoprotein cholesterol (15). Already, new approaches to therapy are being explored that focus on oxidatively-metabolized derivatives of low-density lipoprotein cholesterol which are postulated to exercise a key role in atherogenesis (1, 16).

Even though raised lipid levels do not uniformly promote coronary atherosclerosis in all people (17) there is now little doubt that improving the lipid profile, whether by lipid-lowering drugs, diet (18) or ileal bypass (19), favourably affects the course of atherosclerosis in high-risk patients (20). However, considerably more needs to be known about the clinical consequences of these interventions in the longer term. The task is complicated by the accession of successive generations of lipid-lowering drugs to the market. Increasing usage intensifies the need for sustained, epidemiologically-based surveillance of treated patients.

References


The safety of ivermectin in pregnancy

The decision to release an entirely new antiparasitic drug for administration on a community basis in rural Africa sets a particular challenge to the innovating company and to drug regulators alike. Reliable objective evidence on the performance of the drug, and particularly on its safety when used in the field is unlikely to emerge unless a concerted effort is made at the outset to maintain comprehensive records on a large cohort of treated patients that will provide a resource for prospective epidemiological investigation. This is a need that was recognized when ivermectin was introduced for community-based treatment of onchocerciasis in West Africa and the measures that were taken have set a rigorous standard for post-marketing surveillance under field conditions.

The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases together with the United States National Institutes for Health have collaborated with the manufacturer in supporting a series of large-scale projects designed to assess the efficacy and safety of ivermectin when delivered annually as a single oral dose of 150 micrograms/kg. Encouraging results were rapidly reported on the acceptability of this regimen and on its effectiveness in suppressing the microfilaraemia responsible for the major clinical manifestations of the disease (1-3). Longer-term studies undertaken over a period of 3 years within a community of 14,000 treated workers and their families living on a rubber plantation in the tropical rain forests of Liberia, have now shown that regular annual distribution of ivermectin may substantially reduce the transmission of infection (4).

It is vital, however, to obtain direct assurance that this striking benefit is obtained without inadmissible risk. In particular, evidence must be obtained that a drug likely to be offered to young adults throughout their reproductive lifespan has no demonstrable teratogenic activity. In default of this evidence, every effort has thus far been taken to withhold ivermectin from women during pregnancy, when necessary by establishing the dates of the last menstrual period.
Notwithstanding this precaution, about half the women enrolled in the Liberian study received ivermectin while they were in the first trimester of pregnancy (5). In all, 203 children were identified as having been exposed before birth. The incidence of major congenital malformations in children born both to treated and untreated mothers was about 2.5 per cent, a figure comparable with rates previously reported in the population at large in Africa (6), and no differences were apparent between the types of defects recorded. The sample size was adequate to detect a 4 per cent rise in the incidence of major congenital malformations with a certainty of 90 per cent but it was not adequate to detect small changes in any specific malformation.

The study provides important assurance about the safety of ivermectin and, in doing so, it will help to define future strategy in implementing large-scale mass treatment programmes to control onchocerciasis. At the same time it provides a salutary warning that there is no practicable and reliable means of screening out women in early pregnancy from mass-dosage chemotherapy campaigns. Having regard to the large proportion of children likely to be exposed to ivermectin before birth when it is administered on a community basis, further surveillance is needed — and the lesson must be extrapolated to other drugs destined to be used in similar circumstances.

References


Failure of antimony regimens in advanced mucosal leishmaniasis

Cutaneous leishmaniasis, which is transmitted by sandflies from forest rodents and sloths, is endemic throughout Central America and the northern half of South America. It is estimated that in Costa Rica, for example, some 2,000 new cases occur each year within the total population of about 2 million (1). In a small number of these patients mucosal lesions subsequently develop deep in the mouth and the nasopharynx, often many years after the cutaneous lesions have healed. Sometimes they remain indolent for years, but they can become relentlessly progressive, resulting in septal perforation, loss of the uvula, palatal adhesions, tonsillar fibrosis and laryngeal constriction leading occasionally, in extreme cases, to suffocation (2, 3).

WHO tentatively recommends that these patients should be treated with pentavalent antimony for 28 days at a high dosage providing 20 mg antimony per kg of body weight daily (4). Similar regimens were known to be effective in the majority of cases of cutaneous and visceral leishmaniasis (5, 6), but the long-term results of treating mucosal lesions had never been securely established. Relevant data have now been reported from a study involving 29 consecutively-diagnosed Peruvian patients with mucosal lesions attributed to L. braziliensis braziliensis (3). The initial responses to antimony in the form of sodium stibogluconate were promising. Over 90 per cent of the lesions either healed or were considerably improved and 18 of the patients were considered cured both clinically and parasitologically. It has since become evident, however, that the regimen has little lasting value once the disease has become severe. Nineteen of the 21 patients with advanced lesions relapsed within one year, whereas 6 of 8 patients with early to moderate lesions remained disease-free.

The authors acknowledge that yet higher doses of antimony have been reported to be effective in the management of patients with mucosal (7) and visceral disease (6, 8). But they question whether this can safely be recommended for general use. Hepatic and cardiac adverse effects were prominent among their patients and in 3 cases treatment had to
be discontinued prematurely. They call for further information on the toxicity and tolerability of high-dose antimony regimens and for comparative evaluations with other potential treatments. They also point to the possibility of using antimony in lower dosage together with other less potent antileishmanial compounds, such as allopurinol, ribonucleoside or ketoconazole, or with an immunostimulant such as interferon gamma. Not least, they suggest that further attention might well be directed to amphotericin B which, 20 years ago, was reported to have an effect on mucosal lesions at least comparable to that of the antimonials (9, 10).

References


Oral contraceptives: the significance of metabolic effects

It is the progestogen component of combined oral contraceptive preparations that is primarily responsible for preventing pregnancy. Concerns have long been expressed that at least some of the progestogens that are employed for this purpose may also influence lipid and carbohydrate metabolism in a way that promotes risk of coronary heart disease (1, 2). The changes that have been reported include rises in serum triglyceride and low-density lipoprotein cholesterol, falls in high-density lipoprotein cholesterol, impairment of glucose tolerance and raised plasma insulin levels (3).

As yet, the contribution of these metabolic changes to the incidence of premature coronary heart disease and myocardial infarction among regular users of these products is uncertain (4). Indeed, the epidemiological evidence linking their use with an increased risk of cardiovascular disease remains controversial (5–8). Even so, it is obviously prudent to establish the "metabolic profiles" of various types of widely-available combined contraceptives and, other considerations being equal, to prescribe preferentially those that are least associated with risk factors for these diseases.

A survey of changes produced over a period of 3 months in plasma lipoprotein concentrations and in glucose tolerance by 9 types of oral contraceptive in a sample of over 1000 women and 400 control subjects has now provided an objective basis for formulating this choice (9). Low-dose progestogen-only formulations induced only minor metabolic changes. Among the combined preparations — each of which contained 30 to 40 micrograms of ethinylestradiol — those containing the relatively new progestogen, desogestrel, or low doses of norethisterone, were associated with the most favourable profiles. Some of the other preparations increased serum triglyceride levels in amounts ranging up to 75 per cent and those containing levonorgestrel also significantly reduced levels of high density lipoprotein cholesterol. All combined preparations impaired glucose tolerance by some
40 to 60 per cent, while insulin and C-peptide responses were impaired in somewhat lesser degree. The differences in the magnitude of the metabolic effects associated with the different preparations are large given the low doses of progestogens that are currently employed in combined preparations, and they are clearly sufficient to warrant detailed epidemiological investigation.

References


Vitamin A: malnutrition and infection

Despite strenuous efforts that have been made throughout the past decade to reduce the burden of infection among the very young in the least developed countries (1), acute infection superimposed on chronic malnutrition accounts for the great majority of deaths in early childhood in many developing countries (2-4). Emphasis has been placed on the protective value of breast-feeding. The prevalence of measles, pertussis and other frequently lethal childhood infections has been reduced substantially in many communities through the development of effective national immunization programmes. Several of the most prevalent diseases, including diarrhoea and lower respiratory tract infections, are now generally better managed within primary health care systems. Too often, however, hard-won progress has been more than offset by worsening nutritional status resulting from deepening economic recession or crop failure.

Thus far, most interventions to restore dietary sufficiency have been directed to satisfying protein and energy requirements. Less attention has been accorded to targeted interventions with micronutrients, with the notable exceptions of iodine and vitamin A. The latter first gained attention through its striking effect in preventing blindness due to malnutrition. When it was first discovered early in this century, vitamin A was recognized also to protect animals from infection (5), but epidemiological evidence for such an effect in man has only been obtained in the past few years (6-9).

The first such studies, which were undertaken in Indonesia, indicated that deficiency of vitamin A, even in mild degree, is associated with increased morbidity and mortality in children, largely as a result of vulnerability to diarrhoea and respiratory infection (7, 8). These findings were consonant with evidence obtained from animal studies undertaken many years earlier which showed vitamin A deficiency impairs epithelial integrity, not only in the conjunctiva, but also in the respiratory and intestinal tracts (10). Further evidence of a protective effect was obtained in a clinical context when it was estimated that overall mortality was reduced by some 30 per cent among children at risk when severe vitamin A deficiency was corrected by administering supplements on a community basis (11).

Confirmation of the beneficial effect of vitamin A in children has since been obtained in other settings (3, 4). In an independent study undertaken in Indonesia, a comparable reduction in mortality was recorded in an independent study among children who received a dietary supplement of monosodium glutamate to which vitamin A had been added (12). An even more impressive fall in mortality was recorded among children in southern India who received the physio-
logical requirement of Vitamin A in regular weekly doses (13).

Not all the evidence points to the same conclusion, however. Another prospective, double-blind, placebo-controlled community study undertaken in southern India (14) that involved 15,000 children has confirmed that mild xerophthalmia is a risk factor for respiratory infection — as had been demonstrated in an earlier retrospective study undertaken in India (15) — but vitamin A supplementation of 200,000 IU every 6 months had no demonstrable effect either on mortality or any other index of morbidity. It has been suggested that these largely negative results may simply reflect unreliable dosing or a muting of the impact of vitamin A on mortality resulting from greater attention to immunization and early treatment of infection (3).

Further information to corroborate the importance of vitamin A in protecting children against infection has been obtained in randomized studies conducted in Tanzania (16) and South Africa (17). Each recorded a reduction in mortality from severe measles among hospitalized children given a supplement of vitamin A at the time of diagnosis in a total dose of 400,000 IU over 2 days. These results are of particular interest since, whereas the deficiency was commonly severe among the Tanzanian children, it was largely marginal among the children included in the South African study.

It was estimated 10 years ago that, within Bangladesh, India, Indonesia and the Philippines combined, about 500,000 young children develop xerophthalmia annually as a result of severe vitamin A deficiency (18), of which only 30 per cent survive and half of whom are permanently blinded (19). The more recent findings now leave no doubt that deficiency, in lesser degree, also constitutes a risk factor for mortality from measles and, perhaps, from respiratory and other infections. Individual governments hold a responsibility to establish whether they are confronted by vitamin A deficiency on a scale and of a severity that merits intervention and, if so, whether the deficiency can be corrected most effectively by dietary adjustment or by supplements (20). WHO recommends, as the preferred strategy, improved dietary intake as well as control of infections — especially measles, diarrhoea, and acute respiratory infections — which aggravate vitamin A deficiency in early childhood. It recognizes, however, that a supplement, taken as a single capsule of 200,000 IU at 6 month intervals, offers an alternative approach to the correction of deficiency in many areas where xerophthalmia is common, and that routine administration to children with measles wherever the case-fatality rate is raised can be expected to save many lives (21).

References


which remains active in the residual clot and in the survival (1). Anticoagulant therapy with heparin also thrombolytic process at low dosage by inhibiting the thrombus (3). Acetylsalicylic acid accelerates the thrombolytic agents which recanalize the occluded artery by dissolving fibrin within the coronary thrombus (3). Acetylsalicylic acid accelerates the thrombolytic process at low dosage by inhibiting the aggregation of platelets and, even when given alone, it has been shown to improve the prospect of survival (1). Anticoagulant therapy with heparin also hae a contribution to offer since adsorbed thrombin, which remains active in the residual clot and in the adjacent vessel wall for some days after the initial occlusion, is almost certainly the principal cause of early reocclusion and reinfarction (4). As yet, however, acute cardiac infarction still claims many deaths. Rapid initial recanalization is not always achieved, reocclusion occurs within hours or days in as many as 10 per cent of patients and, in a smaller number, spontaneous bleeding is troublesome and sometimes dangerous (4).

Substantial improvement in therapy may one day stem from the development of more precisely targeted anticoagulant and antiplatelet drugs (5). Heparin is but a weak inhibitor of thrombin, while acetylsalicylic acid not only suppresses the synthesis of prostaglandins that promote platelet aggregation but also of those that inhibit the process. Meanwhile, however, there should be no doubt about how the antithrombotic effect can be most effectively sustained in the immediate post-infarction period with the drugs currently available. Provision of this clarification has been the objective of several recent multicentre trials that have compared the results obtained with acetylsalicylic acid, with intravenous low-dose heparin, and with both in combination.

In one randomized study undertaken in the United States (6), 200 patients who presented within 6 hours of the first sign of occlusion received an immediate intravenous infusion of alteplase. This was followed, for the next 7 days, either by acetylsalicylic acid, 80 mg daily, or by intravenous infusions of heparin adjusted, after initial loading, to lengthen the partial thromboplastin time 1.5 to 2-fold. Coronary angiograms performed towards the end of the first day revealed that the involved vessel remained patent in more than 80 per cent of the patients who were receiving heparin, but in only half of those taking acetylsalicylic acid. Subsequently, the two treatments provided similar protection. After 7 days, a further angiogram showed that, within both treatment groups, about 90 per cent of the vessels patent on the first day still remained open.

Comparable studies have been reported in abstract by two other groups, one in Europe and the other in Australia. In the former, consonant results were obtained when heparin and acetylsalicylic acid were both administered concurrently throughout the first seven days (7). In the second, 200 patients received alteplase followed by intravenous heparin for 24 hours before they were randomly assigned either to continue receiving heparin or to transfer to acetylsalicylic acid and dipyridamole (8). After 7 days no significant treatment-related differences were

More on acetylsalicylic acid and thrombolysis

Prompt intravenous infusion of either alteplase (TPA), streptokinase or anistreplase considerably reduces the immediate mortality resulting from acute myocardial infarction (1, 2). Both substances are thrombolytic agents which recanalize the occluded artery by dissolving fibrin within the coronary thrombus (3). Acetylsalicylic acid accelerates the thrombolytic process at low dosage by inhibiting the aggregation of platelets and, even when given alone, it has been shown to improve the prospect of survival (1). Anticoagulant therapy with heparin also hae a contribution to offer since adsorbed thrombin, which remains active in the residual clot and in the


evident. About 80 per cent of the involved coronary arteries in both groups of patients were shown on angiography to have remained patent.

Taken together, these findings suggest that anticoagulation with heparin during the first 24 hours after initial thrombolysis substantially reduces the risk of reocclusion. However, its subsequent withdrawal in favour of oral acetylsalicylic acid simplifies management without apparently placing the patient at demonstrable disadvantage.

References


Anticoagulation in nonrheumatic atrial fibrillation

The need for anticoagulant therapy in patients with atrial fibrillation related to valvular heart disease is well defined, but the value of prophylaxis when the dysrhythmia results from other causes has long been contested, even though the condition may be associated with as many as one half of all embolic incidents of cardiac origin (1-4). In the elderly, atrial fibrillation has been claimed to carry an annual risk of ischaemic stroke of 5 per cent or more. Clinicians, however, are wary of committing elderly patients to prolonged anticoagulant therapy without firm assurance that the benefits decisively outweigh the hazards of spontaneous bleeding.

This assurance now seems to have been provided. Three prospective multicentre randomized studies — one undertaken in Denmark (5, 6) and the others in the United States of America (7, 8) — have together generated data that establish both the protective value and the relative safety of long-term low-dose warfarin therapy in nonrheumatic atrial fibrillation. In the most recent of these trials, half of some 400 patients — with a mean age of 68 years on admission to the study — received warfarin for an average period of 2 years in a dose sufficient approximately to double the prothrombin time. About 10 per cent of patients voluntarily discontinued treatment before the end of the trial. Of the remainder, ischaemic strokes were recorded in 2 patients receiving warfarin and 13 in the control group. The overall death rate was also substantially higher within the control group. Spontaneous haemorrhage did not present a serious problem. Whereas an excess of minor bleeding episodes was noted among patients receiving warfarin, none required hospitalization.

The careful and sustained monitoring that must be accorded to patients receiving warfarin generates costs that, in many countries, cannot be met by individual patients or by public health services. The question then arises as to whether acetylsalicylic acid, which reduces platelet adhesiveness, holds value as an alternative. Within the context of the Danish trial, a dose of 75 mg daily was judged to be without benefit (5). Even 325 mg daily, which was taken on a self-selecting basis by some control patients in the study described above, has been considered ineffective. However, in the other US study — in which the design provided for a more rigorous assessment — the same dose was reported to be of value, especially among patients aged less than 70 years (7).

The possibility has been raised that these disparate results reflect not so much variations in dosage and experimental design, but the varied causes of atrial
fibrillation (9). In the presence of an enlarged left atrium, stasis is presumed to generate emboli by favouring the formation of fibrin. In these circumstances, if platelet activation is not prominent, acetylsalicylic acid will not be effective. Conversely, turbulence produced by a structural abnormality of the mitral valve will generate thrombi largely as a result of platelet activation — an effect which should be at least partly suppressed by acetylsalicylic acid. There is clearly scope for further investigation of the potential value of acetylsalicylic acid to the very large numbers of patients with atrial fibrillation who will never experience the benefits of warfarin therapy.

References


General Information

Pricing of pharmaceuticals

The ever-spiralling costs of new drug development and the pricing arrangements by which these costs are ultimately passed on to the consumer is a matter for perennial debate among health professionals, patients, politicians and the general public alike. The research-based industry, none the less, stands firmly by its claim that, within many highly developed countries, the proportion of the gross national product devoted to prescription sales has stayed small and constant over the past 25 years (1). Overall, however, the costs of medical care have increased substantially at a time when distribution of wealth has changed dramatically. Widening differentials between the affluent and the deprived are apparent everywhere: between countries, between individuals, and between allocations made to major government departments. The result, even in many countries where public health insurance has long been provided, is that rationing of health care has become entrenched in the public sector and medical costs are quickly impoverishing increasing numbers of people. As many of the world’s major economies plunge yet again into recession, accentuation of these unwelcome trends seems inevitable.

None of this is within the province of pharmaceutical companies to change, but since the initial dosage costs of innovative medicines can sometimes exceed the median annual per capita income in the countries in which they are registered, it is reasonable to expect a generous measure of transparency in price-setting within the industry. A leading article in the American Journal of Hospital Pharmacy acknowledges that the innovative capacity of pharmaceutical companies has shaped the practice of modern medicine, and it assures the industry that reasonable people understand and accept that its success has been built on the sale of medicinal products (1). This being so, it argues, companies would be well served if they explained more forthrightly how they determine the prices of their products. Until they do so, the article warns, suspicion and conjecture will continue to flourish as to the industry’s pricing methods and motives.

The price of zidovudine, still the only drug licensed for the treatment of acquired immunodeficiency syndrome (AIDS), continues to fuel and animate the debate (2). It is estimated that sales of the drug have already reached some US$ 700 million in the United States of America alone. Initially, the average annual prescription cost for each patient was approximately US$ 10 000. Some respite has since been gained, partly through a reduction in the recommended daily dose and partly through a 60 per cent reduction in the unit price. Companies challenging the manufacturer’s patent confidently predict that the product could still be marketed profitably at less than half the current price (2).

Strenuous attempts, it seems, are in the offing to wrest control of the drug from the current owners but there is a recognition within the AIDS community that “strong arm tactics used by activists and legislators alike may send a worrying signal to the rest of the industry” (2). If momentum in the search for a cure for the disease is to be maintained, whichever company ends up manufacturing the drug must be allowed a fair profit. “Just how much profit is fair, and who should decide” are questions that cannot fail to attract attention in the current climate of opinion. An industry confident of its products and of its record of service to the community should not hesitate in contributing objectively and openly to the debate.

References


Teratology information services

A comprehensive approach to drug surveillance must involve a variety of different inputs. A broadly-based spontaneous reporting system needs to be complemented and supported by various specialized data bases and reference centres. Information on congenital deformities needs to be gathered systematically and organized in such a way as to permit assessment of reproductive risk associated not only with drugs but with other potential teratogens in the environment. To meet this need within
Europe, efforts have been directed over the past 15 years to establishing a network of national teratology information services and, in 1990, an international coordinating centre was established in Italy.

Experience gained within two of the longest-established centres, situated respectively in Lyon, France, and Bilthoven, Netherlands, has been briefly reviewed in a recent issue of *Teratology* (1). The French centre runs a birth defects monitoring system that handles some 90,000 reports annually. Even this impressive number has proved to be too small to signal newly-suspected hazards with reliability. A practicable basis for pooling data from the various national centres is urgently needed but further standardization of data entry and criteria of assessment are required before the objective can be realized.

Ultimately, it is anticipated, a fully integrated database should enable the coordinating centre to identify drugs that have proven, through extensive clinical use, to have little or no teratogenic potential. As yet, however, the centres are largely occupied in responding to requests for information from individual doctors. Their search facilities provide rapid access to published information, including relevant epidemiological studies and case reports, and their capacity to respond is extended through close working relationships that have been forged with poisons control centres and national and regional drug monitoring centres.


**Hypercalcaemia and cancer**

About one in 10 patients with terminal cancer develops hypercalcaemia. Sometimes this results from the growth of metastases in bone and sometimes from anomalous production by the primary tumour of peptide regulatory substances that stimulate osteoclastic activity. The significance of this to the patient is that high plasma concentrations of calcium often induce nausea, vomiting, constipation and an excessive output of urine. As concentrations increase, further mental function is impaired and, in extreme cases, death occurs.

A reduction in the circulating level of calcium does not necessarily prolong life in these circumstances but it can considerably improve its quality in the last weeks or months. This important aspect of terminal care has been reviewed in a recent issue of the *Drug and Therapeutics Bulletin* (1). It advises that patients with mild, asymptomatic hypercalcaemia should be encouraged to drink 3-4 litres of fluid daily and that serum calcium should be checked every 4 weeks. The immediate need for patients with symptoms is intravenous rehydration with isotonic saline. This not only restores extracellular volume, it also induces a sodium-linked calcium diuresis. Further forcing of diuresis with furosemide can augment the rate of calcium excretion, but more intensive monitoring is required and the likelihood of inducing hypokalaemia requiring correction with potassium supplements is increased.

Various approaches have been used to prevent subsequent relapse. Until recently, these had been largely ineffective or unacceptably dangerous. Low calcium diets and orally administered calcium-binding agents are of no avail since gastrointestinal absorption is largely suppressed when serum levels are raised. Infusions of sodium edetate have only a transient effect and they can impair renal function. Prednisolone has been widely used, but even in high doses it is ineffective unless the tumour itself is steroid sensitive.

Administration of intravenous neutral phosphate rapidly reduces serum calcium, but it has caused hypotension and irreversible renal failure. Phosphate can also be effective when administered orally at a dose of 2-3 g daily, but, since it commonly causes gastro-intestinal intolerance, it has limited practical application.

Several drugs, including gallium nitrate, calcitonin and plicamycin, have a specific inhibitory effect on osteoclastic activity. However, the first two are limited in their efficacy when used alone and the last — a cytotoxic agent formerly known as mithramycin — has caused thrombocytopenia and hepatic and renal damage. Of greater potential are the biphosphonates, of which three salts — clodronate, etidronate and pamidronate — have now been registered in several countries. All need to be administered intravenously, but preliminary studies indicate that the response to each course of treatment is typically sustained for 2 to 3 weeks. As yet, the treatment costs remain high, and more needs to be known about the range of tumours that are responsive but, on the evidence currently available, they seem to be reasonably tolerated and to represent an important advance in therapy.

Prevention of bacterial endocarditis

The American Heart Association has recently updated its recommendations for the prevention of bacterial endocarditis (1). Recognition that poor dental hygiene can result in bacteremia even in the absence of dental intervention is strongly emphasized. Anyone at risk of bacterial endocarditis is advised to maintain the best possible oral health and to tell their dentist of their need for prophylactic antibiotics before any procedure likely to cause gingival bleeding is undertaken. Dentists are also advised that painting chlorhexidine on the gingiva a few minutes before tooth extraction can reduce the intensity of the initial bacteremia.

Alpha-haemolytic streptococci are the organisms most commonly responsible for endocarditis following dental and other interventions on the oropharynx and upper respiratory tract. They are highly susceptible to amoxicillin, ampicillin, and phenoxyethylpenicillin in vitro. However, amoxicillin has the advantage that it is better absorbed and provides higher and longer sustained serum concentrations. The recommended standard regimen is 3.0 g orally 1 hour before the procedure, followed by 1.5 g 6 hours later. Erythromycin — either as the ethylsuccinate or the stearate — is recommended for patients allergic to penicillins. When this, in turn, is not tolerated, clindamycin hydrochloride is suggested.

Parenteral regimens are no longer proposed for patients who are at particularly high risk of endocarditis since appropriate oral regimens have been shown to be comparably effective. Ampicillin sodium is recommended for patients unable to take drugs by mouth. Parenteral amoxicillin is not available in the United States. An intravenous or intramuscular injection of 2.0 g ampicillin is given 30 minutes before the procedure followed by 1.0 g 6 hours later. Clindamycin, administered as the injectable phosphate salt, is again suggested as the alternative for patients allergic to penicillins. Parenteral regimens are no longer proposed for patients who are at particularly high risk of endocarditis since appropriate oral regimens have been shown to be comparably effective. Ampicillin sodium is recommended for patients unable to take drugs by mouth. Parenteral amoxicillin is not available in the United States. An intravenous or intramuscular injection of 2.0 g ampicillin is given 30 minutes before the procedure followed by 1.0 g 6 hours later. Clindamycin, administered as the injectable phosphate salt, is again suggested as the alternative for patients allergic to penicillins.

Endocarditis resulting from open heart surgery is most often caused by Staphylococcus aureus, coagulase-negative staphylococci, or diphtheroids. Streptococci, Gram-negative bacteria and fungi are less common. No single antibiotic regimen is effective against all these organisms, and prophylaxis should be directed primarily against staphylococci. In most cases, a "first generation" cefalosporin is appropriate, but vancomycin may be required if there is known to be a high prevalence of meticillin-resistant S. aureus within the institution. To reduce the risk of emergence of resistant organisms, cover with these antibiotics should be extended beyond 24 hours.

Endocarditis is likely to be particularly severe among patients with prosthetic heart valves. Mortality is high and the risk appears to continue indefinitely. For these patients, rigorous prophylaxis whenever there is risk of bacteremia can never be relaxed.


Gram-negative sepsis and monoclonal antibodies

Gram-negative bacteremia and sepsis due predominantly to systemic infection with Escherichia coli, Klebsiella, Pseudomonas aeruginosa, Serratia marcescens or Bacteroides fragilis is common among hospitalized patients (1, 2). Because it typically occurs in patients who are already seriously ill and is sometimes difficult to confirm by culture, its incidence is difficult to assess accurately, but recent surveys undertaken in the United States suggest
that the number of cases have increased sharply over the past decade (3). Mortality is high and, in the individual case, the outcome is strongly influenced by the age and physical condition of the patient, and the presence or absence of shock (4-6). Once shock supervenes, the risk of a fatal outcome has been claimed to be as high as 90 per cent (5).

The mechanism of shock is complex. Initially, endotoxin — a lipoprotein component of the bacterial cell wall — is shed into the circulation (8, 9). Part of this substance, the lipid A moiety which is common to all Gram-negative bacteria, is immunogenic (10). This exerts its biological action by releasing two primary mediators, the endogenous pyrogens tumour-necrosis factor and interleukin-1, from monocytes and macrophages (11, 12). In turn, these stimulate the release of a cascade of secondary mediators, including prostaglandins, endorphins, leukotrienes and interferons, from endothelial and inflammatory cells (10). The resulting physiological responses of inflammation, vasodilation, increased vascular permeability, myocardial depression, disturbance of clotting mechanisms, bronchoconstriction and direct tissue necrosis, constitute the basis of the bacterial sepsis syndrome (13).

No single antimicrobial regimen is effective against all the organisms responsible for Gram-negative sepsis. Whereas appropriate antibiotic therapy can improve the prospects of survival when given early (4) it has been claimed that, in practice, overall mortality rates for these infections have not changed since the 1950s (14). Important advances in the development of broad-spectrum antibiotics, including the introduction of beta-lactams, carbapenems and quinolones, have had little impact on the mortality associated with these infections.

It is this singular lack of success of antibiotic treatment that has recreated the stimulus to explore the potential of serum therapy for these infections (15). The basic idea was developed 100 years ago when von Behring established the foundations of immunology by giving patients with diphtheria an antibody raised in horses. Although occasional successes were recorded with sera raised against pneumococci and other specific microorganisms, interest in the approach was lost as a result of the spectacular impact of antibiotics on the management of acute bacterial infections in the 1940s.

Over the previous half century several problems had frustrated the advancement of serum therapy. The antibodies then developed recognized and inactivated only the specific organism used to raise them.

Extraneous allergic material frequently induced anaphylactic reactions and the difficulty of maintaining a bank of representative sera was formidable. Many of these difficulties have become manageable as a result of advances in molecular biology. Not only can antibodies now be raised against specific epitopes of selected bacteria, they can be generated in large quantities and in highly purified monomeric form in hybridoma cells (mouse splenocytes fused with myeloma cells) that can be grown indefinitely in culture (16, 17). This technology has wide application. It has already been exploited with success in other fields including the development of diagnostic reagents designed to detect and identify pathogens and tumour-related antigens, and in the development of immunosuppressant drugs and anti-cancer agents.

Its potential in the treatment of Gram-negative infections has now been explored for more than ten years. Results obtained from the early studies were encouraging but sometimes inconsistent (15, 17). The research has since been given impetus, however, by the production of a monoclonal antibody directed against a portion of Gram-negative endotoxin known as lipid A. This was originally derived from E. coli, but it is cross-reactive to endotoxin from many pathogenic Gram-negative organisms. Preliminary accounts of a multicentre collaborative study involving almost 500 patients who, in addition to receiving appropriate antibiotics and supportive care, were randomly assigned to monoclonal antibody or placebo are claimed to be encouraging. No serious allergic reactions were reported and the mortality among patients who had Gram-negative sepsis but were without signs of shock was “significantly” decreased within the antibody-treated group (17, 18).

The way is now open, it seems, for the development of monoclonal antibodies directed not only against other lipopolysaccharides from Gram-negative bacteria but against soluble mediators involved in the septic-shock cascade in the hope that one or more might be effective in the more advanced phases of these infections.

References


Regulatory Matters

Acitretin: confusion over the teratogenic risk

Acitretin, a new derivative of retinoic acid, has recently been registered in several European countries for the systemic treatment of severe forms of psoriasis. Like etretinate, which is also widely available for this purpose, it is a potent teratogen. Its much shorter half-life was considered to confer advantage since it was assumed that contraceptive precautions would need to be maintained for only 2 months after the last dose — as compared with the 2-year period stipulated following treatment with etretinate.

However, preliminary chemical analyses now suggest that in some patients acitretin is partially metabolized to etretinate. All national drug regulatory authorities that have registered acitretin have been informed of this finding and the manufacturer has requested that all pending applications for registration be suspended.

While awaiting further information the French health ministry has decided to suspend the product licence for acitretin and to reinstate etretinate. Acitretin remains available in other countries where it was previously registered on the understanding that the minimum post-treatment period of contraception stipulated in the product information will be extended to 2 years, and that all women currently using the product will be informed immediately of this action.

Sources
2. Communication from the Directorate of Pharmacy and Medicine, Paris, France, 31 October 1990.

Beclobrate: withdrawal following cases of hepatitis

Switzerland — Products containing the antihyperlipidaemic agent, beclobrate, have been withdrawn from the market following reports of 2 fatal cases of hepatitis. Both patients, who had recently started taking the drug, had previously received other derivatives of fibrin acid without adverse effect.

Source: Communication from the Intercantonal Office for Control of Medicines, Berne, Switzerland, 24 September 1990.

Tighter rules for bioequivalence testing

United States of America — All laboratories in the United States that are engaged in the testing of pharmaceutical products are now required by the Food and Drug Administration to retain samples of the materials that have been tested for at least 5 years. This stems from the discovery that some generic drug companies have either deliberately substituted other manufacturer's products for their own, or wilfully altered batch numbers, when submitting samples for bioequivalence testing. The number of generic drugs marketed in the USA has increased markedly since 1984 following the introduction of the Drug Price Competition and Patent Term Restoration Act which facilitates the approval of generic versions of innovative products that are no longer protected by patent.

In the light of this situation, the FDA has already analysed over 3000 samples of drugs in the distribution chain and it has performed rigorous inspections of 36 manufacturers of generic drugs. About 250 products made by 27 companies have been recalled and over 100 product licences are being withdrawn. Further checks are planned but, at this stage, the FDA has indicated it is confident that generic drugs currently marketed in the USA are safe and effective.


Eflornithine for Gambian trypanosomiasis

United States of America — The Food and Drug Administration has approved the marketing of eflornithine hydrochloride under the provisions of the
Orphan Drug Act. Administered intravenously, it can cure many cases of late-stage Gambian trypanosomiasis. Efficacy against Rhodesian strains of the parasite has yet to be established. The neurological phase of these diseases was previously treatable only with arsenicals which induced fatal encephalitis in as many as 10 per cent of treated patients. Eflornithine does not appear to be neurotoxic. However, a high incidence of leukopenia and thrombocytopenia renders twice-weekly monitoring of the blood count mandatory throughout the period of treatment.


Nitroprusside and cyanide toxicity

United States of America — Sodium nitroprusside was first introduced in 1975 to reduce the blood pressure of patients in hypertensive crisis and to produce a state of controlled hypotension before and during specified surgical interventions. It is highly effective for these purposes, but serious and potentially-avoidable adverse effects are still occasionally reported. These include death or irreversible ischaemic injury resulting from profound hypotension and potentially lethal metabolic acidosis due to cyanide toxicity. The product labelling has consequently been revised with the approval of the Food and Drug Administration to emphasize these risks and to advise clinicians that the initial infusion rate should never exceed 0.3 micrograms/kg/minute. The rate of administration may subsequently be increased gradually, in the light of the clinical response, to a maximum rate of 10 micrograms/kg/minute, but this should not be maintained for more than 10 minutes. If cyanide toxicity is suspected, sodium thiosulfate — which may produce immediate and dramatic improvement — should be infused immediately without waiting for the diagnosis to be confirmed chemically.


Implantable contraceptive system approved

United States of America — The Food and Drug Administration has announced that it has approved the Norplant® contraceptive system for marketing in the USA. The product — which is inserted subcutaneously in the upper arm — contains the progestogen, levonorgestrel, in 6 flexible, tubular, controlled-release capsules. The drug diffuses out in quantities sufficient to inhibit ovulation and render the cervical mucous impenetrable to spermatozoa for 5 years. Throughout this period, the overall cumulative pregnancy rate is estimated to be slightly more than 1 per cent. Somewhat higher failure rates apply after the third year of use among women weighing over 70 kilograms. Doctors are advised that the risks associated with the use of progestogen-only oral contraceptives — including elevated blood pressure, thromboembolic disorders, and other vascular problems — also apply to Norplant®. They are also warned that many patients will experience a change in menstrual bleeding patterns that can mask symptoms of cervical or endometrial cancer.

Advisory Notices

Clozapine-induced neutropenia

United Kingdom — The antipsychotic agent, clozapine, was briefly marketed in several countries in the mid-1970s. It was later withdrawn worldwide in 1977 following the discovery in Finland of its association with several fatal cases of agranulocytosis (1). Within the past year it has been reintroduced in the United States — and subsequently in several other countries — for the treatment of schizophrenia resistant to other therapy. In each of these countries marketing is conditional upon the manufacturer undertaking arrangements to ensure the detection of neutropenia in treated patients before it is likely to have progressed to irreversible agranulocytosis.

In the United Kingdom, patients qualify for clozapine therapy only if they are prepared to enter hospital when treatment is initiated and if their differential white cell count is confirmed to be within normal limits. To obtain further supplies they must be prepared to undergo haematological monitoring every week for the first 18 weeks and every two weeks thereafter (2). Thus far, these precautions have been highly effective. By the end of November 1990, 633 patients had received clozapine. Of these, 13 had developed neutropenia. In each instance the physician was advised of the result within 48 hours and in all cases the white cell count rapidly returned to normal once the drug had been discontinued.

References

Flucloxacillin hepatitis

Australia — The Adverse Drug Reactions Advisory Committee has requested doctors to provide details of any case of hepatitis associated with flucloxacillin that they may have encountered. By November 1990 the Committee had been notified of 73 such cases, half of which had been received within the previous 12 months. Thus far, no predisposing factors have been identified to indicate which patients are most at risk, and the Committee has suggested that an epidemiological study be organized to investigate the problem.


Sodium oxybate: evidence of abuse

United States of America — Sodium oxybate, also known as sodium gamma hydroxybutyrate, is currently available in several European countries as a general anaesthetic for intravenous administration, and is now under clinical investigation in the USA for the treatment of narcolepsy. However, it is also being illicitly promoted and marketed for body building, weight loss, as a psychedelc substance, and as a replacement for L-tryptophan following its recent withdrawal from the market. The Food and Drug Administration has received more than 30 reports of adverse effects attributed to its uncontrolled use, ranging from nausea and vomiting to severe respiratory problems, seizures and coma. It has advised the public of these hazards and it has requested doctors to report all cases of abuse that come to their knowledge to their local poisons control centre.


Mesalazine nephrotoxicity

United Kingdom — A delayed-release formulation of mesalazine (5-aminosalicylic acid) has recently been introduced to maintain remission of ulcerative colitis and to treat mild to moderate exacerbations of the disease.

Mesalazine, like sulfasalazine, is known to be nephrotoxic and this has been confirmed by 9 reports notified to the Committee on Safety of Medicines since February 1988. These included 4 biopsy-proven cases of interstitial nephritis, 3 of severe renal failure and 2 of nephrotic syndrome.
Only three of these patients have, as yet, fully recovered. In the light of this experience, the Committee emphasizes that patients who have either reacted adversely to sulfasalazine or who have established renal impairment should not be treated with mesalazine.


Corticosteroid cover during treatment of pneumocystis pneumonia

United States of America — Despite important advances in prophylactic management, *Pneumocystis carinii* pneumonia causes more deaths than any other opportunistic infection associated with acquired immunodeficiency syndrome (AIDS). More than 40,000 cases were recorded in North America alone in 1990. The risk of fatal hypoxia rises sharply when arterial oxygen tension falls below a critical level of 70 to 80 mmHg (1, 2). The first few days of antimicrobial treatment with trimethoprim-sulfamethoxazole or parenteral pentamidine are particularly critical since hypoxia is often markedly aggravated at this time. This results from an intensified inflammatory response, characterised by mononuclear-cell invasion of the lung interstitium and accumulation of proteinaceous fluid in the alveoli, induced by the death of large numbers of protozoal parasites (3).

Attempts have been made to suppress this reaction with corticosteroids and the results of 4 studies in which controlled observations were made have now been published (3-6). Some 250 patients with presumed pneumocystis pneumonia — which was subsequently confirmed microbiologically in over 85 per cent of cases — were enrolled in the largest of these studies, an open, randomized trial undertaken by the California Collaborative Treatment Group (5). Half the patients received prednisone 40 mg twice daily within 36 hours of starting antimicrobial therapy. This largely prevented further decline in oxygenation during the first three days of treatment and, within the stratum of patients with the lowest oxygen tensions, overall mortality after 31 days was reduced from 43 to 19 per cent. More cases of thrush and herpes simplex infections occurred among the patients who received corticosteroids, but the incidence of other opportunistic infections and Kaposi's sarcoma remained unchanged.

An even greater reduction of mortality was recorded in a smaller trial in which patients with severe pneumonia unresponsive to 3 days antimicrobial therapy received methylprednisolone 40 mg intravenously every 6 hours for 7 to 10 days (6). The study was stopped prematurely when 9 of the control group of 11 patients — but only 3 of 12 patients who received corticosteroids — died before discharge from hospital. A third study has confirmed the benefit of corticosteroids in maintaining oxygen saturation (3). However, in the fourth study, no advantage accrued from 'rescue therapy' with corticosteroids, in which larger intravenous doses were administered selectively to patients in whom specific antipneumocystis therapy had already failed (4).

On the basis of this evidence, national guidelines have been developed (7) which embody the following principles:

- Adults or adolescents with HIV infection and documented or suspected pneumocystis pneumonia should receive adjunctive corticosteroid therapy when the arterial oxygen pressure is less than 70 mmHg or the arterial-alveolar gradient is more than 35 mmHg. The value of corticosteroids in patients with milder hypoxia, in whom the prognosis is relatively good, has not as yet been proven.

- It is reasonable, additionally, to consider using adjunctive corticosteroid therapy to treat pneumocystis pneumonia in immunosuppressed patients without HIV infection and in pregnant women with HIV infection. However, no relevant data are available to enable the efficacy or safety of such treatment to be evaluated.

- Studies of the effects of adjunctive corticosteroid therapy are needed in children under 13 years of age who may differ from adults in their response, both because their immune systems are less mature, and because the infection may be primary rather than reactive.

- Corticosteroid therapy should be instituted as early as possible, preferably at the same time as specific antipneumocystis therapy. Benefit has not been demonstrated when adjunctive therapy has been delayed for more than 72 hours.
• Prednisone 40 mg twice daily should be given orally for the first 5 days, followed by 40 mg daily for 5 days, and 20 mg daily for a further 11 days. When parenteral treatment is necessary intravenous methylprednisolone should be given at 75 per cent of the oral dosage regimen. Higher doses may possibly be beneficial for patients who have failed to respond to standard antipneumocystis therapy administered either alone or in combination with standard adjunctive corticosteroid regimens, but this remains unproven.

References


Zopiclone and neuropsychiatric reactions

United Kingdom — The Committee on Safety of Medicines has advised doctors that, although the new cyclopyrrolone hypnotic, zopiclone, differs structurally from the benzodiazepines, it has the same potential for adverse psychiatric reactions, including dependence. Some 25 such cases have been reported since the product was first launched in the United Kingdom in November 1989. Most of these reactions became evident immediately or shortly after administration of the first dose and they resolved rapidly on withdrawal of the drug. Among those that were potentially serious were 5 cases of auditory or visual hallucinations, 4 cases of amnesia, and 10 cases of behavioural disturbance including 3 of aggression. Three patients found it difficult to stop treatment, 2 because of withdrawal symptoms and one because of repeated rebound insomnia.

**Essential Drugs**

**Cholera: the need for preparedness**

In the early 1960s cholera was endemic only in southern Asia. It has since spread widely and has emerged in epidemic form in at least 100 countries.

Where the disease is present, but not epidemic, it accounts for less than 5 per cent of all cases of acute diarrhoea. Most of these cases are mild and they are often difficult to distinguish from other forms of acute diarrhoea. None the less, cholera constitutes an important public health problem because it has the potential to spread rapidly in unprepared communities and during epidemics it causes many deaths. Although the mortality rate can sometimes approach 50 per cent, well-organized administration of treatment could reduce this to less than 1 per cent.

Only one of more than 60 known serogroups of *Vibrio cholerae* is pathogenic to man. Two biotypes are described — classical and 'El Tor'. The former is essentially confined to the Indian subcontinent and survives for only a short period of time in water, nightsoil and sewage. It is the El Tor biotype, which survives as a free-living organism, perhaps in association with aquatic plants and animals, that has caused nearly all recent outbreaks of the disease. Virtually all these outbreaks have been traceable, directly or indirectly, to fecal contamination of water supplies. Common sources of infection include:

- drinking water that has been contaminated in an inadequately sealed well or during storage.
- fish and shell fish taken from contaminated water and insufficiently cooked.
- leafy vegetables that have been “freshened” with contaminated water.
- contaminated foods that have subsequently been stored unrefrigerated.

When ingested, the organisms adhere to and subsequently colonize the small intestine. Enterotoxins, which stimulate the secretion of water and electrolytes, are responsible for the abrupt onset of painless, "rice water" diarrhoea. Several litres of fluid may be lost within a few hours. In severe cases, hypovolaemic shock rapidly supervenes and, left untreated, many patients die from dehydration, uncompensated metabolic acidosis and uraemia.

**Control**

The aim is to eliminate live cholera organisms from drinking water and food through effective sanitation, personal and public hygiene, and sustained vigilance in reporting and treating cases of diarrhoeal disease. In particular:

- safe water supplies must be provided for drinking and washing;
- the public must be informed of the mode of transmission and educated in prevention of diarrhoeal disease; breast-feeding should be encouraged as a means of protecting infants and young children;
- the basic principles of sanitation, particularly those relating to disposal of human waste, personal hygiene and food safety, must be implemented;
- health workers, assisted by other community members, need to maintain a daily record of new cases of diarrhoea, and to report to the designated health officer any increase in the incidence of cases, as well as any case of diarrhoea that results in severe illness or death of a patient older than 10 years;
- mobile teams should be maintained in a state of readiness to support local health services whenever an outbreak is confirmed on bacteriological or epidemiological information;
- a national task force, constituted to monitor and evaluate the control of cholera and other diarrhoeal diseases, should immediately assume responsibility, on confirmation of an outbreak, for establishing treatment centres, training health personnel, procuring and distributing supplies, collecting and reporting information, and for disinfection routines and disposal of the dead.

Vaccination campaigns are wasteful of scarce resources. Not only do the available preparations fail to provide effective protection, but unsafe injection
practices have resulted in transmission of HIV and serum hepatitis. Certification of vaccination against cholera ceased to be a requirement under International Health Regulations in 1973.

Mass chemoprophylaxis is impracticable and has never been successful in limiting the spread of an epidemic. Secondary cases within families are rare during most outbreaks of El Tor cholera. However, selective chemoprophylaxis with tetracycline — or, more conveniently, doxycycline, since only one dose is required — is considered to hold advantage if, on average, one or more of every five close household contacts subsequently becomes infected.

Treatment

Simplification of case management over the past few years has greatly increased the proportion of patients who can be effectively treated. It is now recognized that as many as 90 per cent of patients require nothing more than prompt and adequate oral replacement of the water and electrolytes lost in the diarrhoeal stool and vomitus. Those who are severely dehydrated require intravenous fluids and antibiotics. There is no place for anti-diarrhoeal drugs, anti-emetics, anti-spasmodics, cardiotonic agents or for corticosteroids in the treatment of the disease.

Pre-packaged oral rehydration salts are of particular value when solutions need to be made up for individual patients, particularly in outlying rural areas. In hospitals and health centres, where large volumes are consumed daily, the solution is more economically prepared from ingredients supplied in bulk containers. Patients should be permitted to drink as much water as they wish in addition to that contained in the rehydration solutions, and food should be offered within 3 to 4 hours as soon as rehydration is completed. Continued breast-feeding of infected infants should be encouraged.

Intravenous fluids should be reserved for the initial treatment of severely dehydrated patients who are unable to drink. A compound solution of sodium lactate is ideal for this purpose. Normal saline or half-normal saline solutions may also be used, but they are less effective in rectifying the accompanying metabolic acidosis. Glucose solutions that contain no electrolyte are ineffective and contraindicated. During the course of rehydration, a short course of oral antibiotic therapy should be started as soon as vomiting ceases. This reduces the volume and duration of severe diarrhoea and shortens the period during which cholera vibrios are excreted.

Injectable antibiotics, which hold no advantage, are unnecessarily expensive.

Tetracycline, because of its wide availability and relatively low price, is used as the first-line antibiotic in epidemic situations wherever the cholera vibrio remains sensitive to its action. The urgency of providing treatment at an affordable price is generally considered to override the risk of administering tetracyclines to pregnant women and young children, particularly since treatment rarely needs to be extended beyond 3 days. Doxycycline, a long-acting form of tetracycline which can be administered in a single dose, is considerably more expensive.

Because tetracycline-resistant strains of cholera vibrio are increasing in prevalence, it is important to be aware of sensitivity patterns in nearby areas and to determine the antibiotic sensitivity of newly-isolated organisms, particularly when diarrhoea fails to respond within 48 hours of therapy. The most widely used alternative antimicrobials are trimethoprim-sulfamethoxazole, furazolidone and less frequently erythromycin and chloramphenicol.

ORAL REHYDRATION SALTS
(glucose-salt solution)

<table>
<thead>
<tr>
<th>g/litre of clean water</th>
<th>sodium chloride</th>
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</thead>
<tbody>
<tr>
<td>trisodium citrate</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>potassium chloride</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>glucose (anhydrous)</td>
<td>20.00</td>
<td></td>
</tr>
</tbody>
</table>

Oral rehydration solution is optimally constituted to correct the fluid and electrolyte loss which results from acute diarrhoea in infants, older children and adults.

When glucose and trisodium citrate are not available, these ingredients may be replaced, respectively, by:

<table>
<thead>
<tr>
<th>g/litre</th>
<th>sucrose (common sugar)</th>
<th>40.00</th>
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</thead>
<tbody>
<tr>
<td>sodium bicarbonate</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

Uses

Prevention and treatment of dehydration from cholera and other forms of acute diarrhoea. Severely dehydrated patients must be treated initially with intravenous fluids until they are able to take fluids by mouth.
**Preparation, dosage and administration**

The solution may be prepared either from prepackaged sugar/salt mixtures, or from bulk substances, and water. Care should be taken to ensure that all ingredients are completely dissolved in the correct quantity of clean drinking water.

A solution containing the recommended quantities of sucrose and sodium chloride only may be prepared when the other ingredients are not immediately available.

A rice-based ORS solution may be made by replacing the glucose or sucrose with 50 grams of rice powder. This should be boiled in one litre of water for 5 minutes and the solution allowed to cool before adding the other ingredients.

It is important to administer the solution in small amounts at regular intervals as detailed in the table. For a small infant the requirement is approximately one 5 ml teaspoonful every 1 to 2 minutes.

**Precautions**

Solutions must be freshly prepared, preferably with water that has been recently boiled and cooled.

Accurate weighing and thorough mixing of the ingredients is important. Administration of more concentrated solutions can result in hypernatraemia.

**Storage**

Pre-packaged ORS solutions are widely available. Solutions which have become discoloured should be discarded.

### TETRACYCLINE

capsule or tablet, 250 mg (hydrochloride)

Tetracycline is a broad spectrum antibiotic derived from a species of *Streptomyces* that induces bacteriostasis by inhibiting protein synthesis. It is selectively concentrated in *Vibrio cholerae*.

Absorption from the alkaline contents of the intestine is slow. Peak plasma concentrations occur within 4 hours and decay with a half-life of about 8 hours. Excretion is effected primarily by filtration into the urine. An enterohepatic circulation results in high concentrations accumulating in the liver and bile.

Tetracycline crosses the placenta and is excreted into breast milk.

**Uses**

Treatment of severe cholera and selective prophylaxis.

**Dosage**

Adults: (Treatment and selective prophylaxis) 500 mg four times daily for 3 days.

Children: (Treatment) 50 mg/kg daily in four divided doses for 3 days. (see note below regarding use during pregnancy and early childhood).

**Contraindications**

Known hypersensitivity.

Severe renal impairment.

**Precautions**

Troublesome oesophagitis may be averted if the patient is propped up while swallowing capsules, which should be washed down immediately with a glass of water.

### Approximate amount of ORS solution to give in first 4 hours

<table>
<thead>
<tr>
<th>Age*</th>
<th>Weight</th>
<th>In ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 4 months</td>
<td>Less than 5 kg</td>
<td>200 - 400</td>
</tr>
<tr>
<td>4 - 11 months</td>
<td>5 - 7.9 kg</td>
<td>400 - 600</td>
</tr>
<tr>
<td>12 - 23 months</td>
<td>8 - 10.9 kg</td>
<td>600 - 800</td>
</tr>
<tr>
<td>2 - 4 years</td>
<td>11 - 15.9 kg</td>
<td>800 - 1200</td>
</tr>
<tr>
<td>5 - 14 years</td>
<td>16 - 29.9 kg</td>
<td>1200 - 2200</td>
</tr>
<tr>
<td>15 years or older</td>
<td>30 kg or more</td>
<td>2200 - 4000</td>
</tr>
</tbody>
</table>

* Use the patient's age only when you do not know the weight. The approximate amount of ORS required (in ml) can also be calculated by multiplying the patient's weight (in grams) times 0.075.
  - If the child wants more ORS than shown, give more.
  - Encourage the mother to continue breast-feeding.
  - For infants under 6 months who are not breast-fed, also give 100 - 200 ml clean water during this period.
Time-expired tetracycline capsules or tablets should be discarded. Degraded tetracycline has been reported to induce renal dysfunction indistinguishable from the Fanconi syndrome and skin lesions similar to those of systemic lupus erythematosus.

**Use in pregnancy and early childhood**
Tetracycline is generally contraindicated in pregnancy and during early childhood because impaired calcification can result in abnormal osteogenesis, permanent staining of teeth and also, on occasion, hypoplasia of dental enamel. However, this consideration is often waived in cholera epidemics since other drugs are often not available, and the period of therapy is short.

**Adverse effects**
Phototoxic reactions occasionally result in porphyria-like skin changes and pigmentation of the nails.

Hypersensitivity reactions are rare. Morbilliform rashes, urticaria, fixed drug eruptions, exfoliative dermatitis, cheilosis, glossitis, pruritus and vaginitis are described. Angioedema, anaphylaxis and pseudotumour cerebri have been reported.

**Storage**
Tetracycline capsules, tablets or solution should be kept in well-closed containers, protected from light.

**DOXYCYCLINE**
capsules, 100 mg (as hyclate)

Doxycline is derived from and closely related to oxytetracycline, and shares an identical spectrum of antibiotic activity. It differs from the tetracyclines in that it is more extensively absorbed and more lipid-soluble, and it possesses a longer serum half-life that is independent of the patient's renal status.

**Uses**
Treatment of severe cholera, particularly in patients known to have impaired renal function. Selective prophylaxis during epidemics of cholera.

**Dosage**
*Treatment and selective prophylaxis for adults:*
300 mg in a single dose

**Contraindications**
Known hypersensitivity

[Sulfamethoxazole + Trimethoprim]

**SULFAMETHOXAZOLE + TRIMETHOPRIM**
tablet, 100 mg + 20 mg, 400 mg + 80 mg
oral suspension, 200 mg + 40 mg/5 ml

The two components of this combination product have a similar antibacterial spectrum. They operate synergistically because they act independently on different steps in the enzymic synthesis of tetrahydrofolic acid, an essential metabolic process in susceptible bacteria. The combination is claimed to enhance the bactericidal potency of the individual constituents and to impede the emergence of resistance.

Trimethoprim is absorbed more rapidly and is more widely distributed in tissues than sulfamethoxazole and readily enters the cerebrospinal fluid. Both compounds are extensively bound to plasma proteins. The plasma half-life of both compounds is about 24 hours and each is excreted largely unchanged in the urine.

**Uses**
Treatment and selective prophylaxis of cholera when strains are known to be resistant to tetracycline.

**Dosage**
Adults: 800 mg sulfamethoxazole + 160 mg trimethoprim in two divided doses for 3 days.
Children: 25 mg/kg sulfamethoxazole + 5 mg/kg trimethoprim for 3 days in two divided doses.

**Contraindications**
Known hypersensitivity to sulfonamides.
Severe hepatic or renal dysfunction.

**Precautions**
Treatment should be suspended immediately should a rash, or any other manifestation of sulfonamide hypersensitivity occur.

**Use in pregnancy**
Safe use in pregnancy has not been established. However, during cholera epidemics treatment should not be deferred.
**Adverse effects**
Sulfonamide-induced hypersensitivity reactions, although uncommon, can be severe. They include life-threatening cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Other infrequent reactions include granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura and toxic hepatitis. Occasionally, haemolysis occurs in G-6PD deficient individuals.

**Storage**
Sulfamethoxazole/trimethoprim tablets should be stored in well-closed containers.

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**FURAZOLIDONE**

*tablet, 100 mg*
*oral suspension, 50 mg/15 ml*

Furazolidone is a synthetic antibacterial agent derived from nitrofuran which is bactericidal to *V. cholerae*. Its effect results from disruption of bacterial enzyme systems.

It is poorly absorbed and is inactivated in the intestine. A small amount is excreted in the urine both unchanged and as metabolites.

**Uses**
*Treatment* of cholera and selective prophylaxis when strains are known to be resistant to tetracycline.

**Dosage**
*Treatment and selective prophylaxis:*
Adults: 100 mg four times daily for 3 days.
Children: 4 mg/kg daily in four divided doses for 3 days.

**Contraindications.**
Known hypersensitivity

**Precautions**
Patients with G-6PD deficiency should be observed closely since acute reversible intravascular haemolysis may be induced.

Patients should be warned that the drug may colour the urine brown.

**Use in pregnancy**
Safe use in pregnancy has not been established. However, during cholera epidemics treatment should not be deferred.

**Adverse effects**
Nausea and vomiting are the most common adverse reactions. Acute haemolysis may occur in patients with G-6PD deficiency.

**Drug interaction**
Rarely a disulfiram-like reaction to alcohol occurs. This is characterized by flushing, hypertension, dyspnoea and a sense of constriction in the chest.

**Storage**
Tablets and oral suspension should be stored in tight light-resistant containers and protected from excess heat.

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**Further reading**


Recent Publications

Management of acute diarrhoea in children

Acute diarrhoea continues to claim more than 4 million young lives each year. Many of these children are lost unnecessarily because reliance is placed in anti diarrhoeal drugs rather than in the necessity of promptly replacing water and electrolyte losses. The fundamental message contained in this book is that anti diarrhoeal drugs and antiemetics should never be used for children, since none has proven value, some actually prolong diarrhoea, and some are frankly dangerous.

In recent months pharmaceutical companies have been confronted with hard data regarding the unacceptable risk of fatal paralytic ileus among children treated with antimotility drugs. Some have now withdrawn paediatric formulations of these products from the market in countries where infantile diarrhoea is a major public health problem. This is but one step among many that are needed to assure a more rational approach to the management of this widely misunderstood disease. This book, which is intended not only for officials in national diarrhoea control programmes, but for everyone sharing in the responsibility for the welfare of the children at risk, sets out the principles at issue clearly and unambiguously. Put into practice, the advice it contains can save countless lives.


Specifications for pharmaceutical preparations

When the WHO Expert Committee on Specifications for Pharmaceutical Preparations was first convened, drug quality was assessed and controlled, even in many highly developed countries, largely on one criterion: the compliance of the active ingredients with legally sanctioned pharmacopoeial specifications. Since then, many countries have promulgated legislation that has provided a basis for creating national drug regulatory authorities empowered to implement a more comprehensive panoply of controls based on a system of technical assessment and licensing of individual products, manufacturers and distributors.

It is time, perhaps, to consider changing the designation of this Expert Committee to indicate that, in compliance with changing times, it is now concerned with all aspects of the quality assurance of pharmaceutical products. This is evident from a glance at the contents of the Committee’s thirty-first report. The topics discussed range from the anticipated discussion of technicalities relevant to the updating of The International Pharmacopoeia, to concerns about drug stability, the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce, and WHO’s Guiding Principles for Small National Drug Regulatory Authorities.

Each of these topics is of prime importance to national authorities still grappling with the organization of drug control. Indeed, the Guiding Principles are at the very fulcrum of WHO’s Revised Drug Strategy. They recognize that legislation and administrative practices must be attuned to available resources and not simply derive from adaptation of provisions successful elsewhere but of a complexity that precludes their effective implementation in the country of adoption. They also acknowledge that small authorities must take every opportunity to obtain and use information provided by regulatory authorities in other countries. The report needs to be read by a far wider range of policy-makers and administrators than persons likely to possess a direct interest in pharmacopoeial specifications.

Tablets in the tropics

The high ambient temperatures and humidity that are characteristic of the tropics promote the degradation of many drugs by hydrolysis when they are inadequately packaged and stored. This impairment of quality can result in therapeutic failure — sometimes in serious clinical situations — and in important financial loss when substantial amounts of stock need to be discarded.

For several years the University of Groningen in the Netherlands has been exploring simple, practicable approaches that could help to redress the difficulties. Some of the findings that have resulted from this work have now been published in two handbooks that offer advice on the local manufacture of tablet forms of widely used drugs in tropical areas. Details of some standard tablet formulations are provided which are based on the use of widely-available excipients and that are physically and microbiologically stable. It is emphasized that the advice is not intended to provide a blueprint for setting up local production, but simply to offer ideas that need to be considered in relation to local needs and resources.


The pharmacological basis of therapeutics

The editors of "Goodman and Gilman" have celebrated its 50th anniversary by producing an extensively updated 8th edition. The pace at which advances in molecular biology have both extended pharmacological knowledge and created possibilities for more rational drug design could not have been predicted when the last edition was put to press in 1985. The challenge inherent in maintaining a comprehensive textbook in such a fast developing field is immense. Some sections are inevitably dated before the book arrives on the shelf. None the less, it is reassuring and heartening for everyone involved with teaching and research in pharmacology to know that, amid the plethora of computerised data bases, review journals, specialized newsheets and other ephemera that vie for attention, this pillar of reference remains solidly in place.

International Nonproprietary Names for Pharmaceutical Substances

In accordance with article 3 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances, notice is hereby given that the following names are under consideration by the World Health Organization as Proposed International Nonproprietary Names.

Comments on, or formal objections to, the proposed names may be forwarded by any person to the Pharmaceuticals unit of the World Health Organization within four months of the date of their publication in WHO Drug Information, e.g., for List 64 Prop. INN not later than 31 August 1991.

The inclusion of a name in the lists of proposed international nonproprietary names does not imply any recommendation for the use of the substance in medicine or pharmacy.

Action and Use

The statements in italics indicating the action and use are based largely on information supplied by the manufacturer. The information is meant to provide an indication of the potential use of new substances at the time they are accorded proposed INNs. 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 be neither revised nor included in the Cumulative Lists of INNs.

Proposed International Nonproprietary Names (Prop. INN): List 64

Comprehensive information on the INN programme can be found in: WHO Technical Report Series, No. 581, 1975 (Nonproprietary Names for Pharmaceutical Substances. Twentieth Report of the WHO Expert Committee), ISBN 92 4 120581 4 (price: Sw. fr. 6.5); an account of this publication will be found in Annex 2 of the present List. All names from Lists 1–58 of Proposed International Nonproprietary Names, together with a molecular formula index, will be found in: International Nonproprietary Names (INN) for Pharmaceutical Substances. Cumulative List No. 7, 1988, World Health Organization, Geneva (ISBN 92 4 0560149) (price: Sw. fr. 65.5). This publication consists, in the main, of a computer printout which groups together all the proposed and recommended international nonproprietary names (INN)—in Latin, English, French, Russian, and Spanish—published up to March 1988. The printout also indicates in which of the 58 individual lists of proposed names and 27 lists of recommended names each INN was originally published, and gives references to national nonproprietary names, pharmacopoeia monographs, and other sources. In addition, the list contains molecular formulae and Chemical Abstracts Service registry numbers. For easy reference, national nonproprietary names that differ from INN, molecular formulae, and Chemical Abstracts Service registry numbers are indexed in a series of annexes. A final annex describes the procedure for selecting recommended INN and outlines the general principles to be followed in devising these names. All the textual material published in this volume appears in both English and French.

These publications may be obtained, direct or through booksellers, from the sales agents listed on the back cover of WHO Drug Information. Orders from countries where sales agents have not yet been appointed may be addressed to: World Health Organization, Distribution and Sales Service, 1211 Geneva 27, Switzerland.


2 Other lists of proposed and recommended international nonproprietary names can be found in Cumulative List No. 7, 1988.
<table>
<thead>
<tr>
<th>Proposed International Name</th>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>abanoquilum abanoquil</td>
<td>4-amino-2-(3,4-dihydro-6,7-dimethoxy-2(1H)-isoquinolyl)-6,7-dimethoxyquinoline</td>
<td>C_{22}H_{25}N_{3}O_{4} 90402-40-7</td>
<td>(\alpha_1)-adrenoreceptor antagonist</td>
</tr>
<tr>
<td>acadesinum acadesine</td>
<td>5-amino-1-(\beta)-D-ribofuranosylimidazole-4-carboxamide</td>
<td>C_{9}H_{14}N_{4}O_{5} 2627-69-2</td>
<td>cardiac stimulant</td>
</tr>
<tr>
<td>acidum gadobenicum gadobenic acid</td>
<td>dihydrogen ((\pm))-4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5-)[gadolinate(2-)]</td>
<td>C_{22}H_{28}GdN_{3}O_{11} 113662-23-0</td>
<td>paramagnetic contrast medium</td>
</tr>
<tr>
<td>adapalenum adapalene</td>
<td>6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid</td>
<td>C_{28}H_{28}O_{3} 106685-40-9</td>
<td>antiacne agent</td>
</tr>
<tr>
<td>adozelesinum adozelesin</td>
<td>(7bR,8aS)-N-[2-[4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]indol-5-yl]-2-benzofurancarboxamide</td>
<td>C_{30}H_{25}N_{3}O_{4} 110314-48-2</td>
<td>antineoplastic</td>
</tr>
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</table>
Proposed International
Nonproprietary Name (Latin, English)
Chemical Name or Description, Molecular and Graphic Formulae
Chemical Abstracts Service (CAS) registry number
Action and use

alentemolum
alentemol

(±)-2-(dipropylamino)-2,3-dihydrophenalen-5-ol
C_{19}H_{25}NO 112891-97-1 antipsychotic

aimokalantum
aimokalant

(±)-p-[3-{ethyl[3-(propylsulfinyl)propyl]amino}-2-hydroxypropoxy]benzonitrile
C_{18}H_{28}N_{2}O_{3}S 123955-10-2 antidysrhythmic

ameltolidum
ameltolide

4-amino-2',6'-benzoxyldide
C_{15}H_{16}N_{2}O 787-93-9 anticonvulsant

angiotensinum II
angiotensin II

5-L-isoleucineangiotensin II
The source of the material should be indicated.
C_{50}H_{71}N_{13}O_{12} 4474-91-3 vasoconstrictor

aprikalimum
aprikalim

(−)-(1R^*,2R^*)-tetrahydro-N-methyl-2-(3-pyridyl)thio-2H-thiopyran-2-carboxamide 1-oxide
C_{12}H_{16}N_{2}O_{5}S 92569-65-8 potassium channel activator
<table>
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<tr>
<th>Proposed International Name (Latin, English)</th>
<th>Proposed International Name (Latin, English)</th>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
</tr>
</thead>
<tbody>
<tr>
<td>aprosulate sodium</td>
<td>aprosulate sodium</td>
<td>$C_{27}H_{34}N_{2}Na_{16}O_{70}S_{16}$ 123072-45-7, anticoagulant</td>
<td>$C_{27}H_{34}N_{2}Na_{16}O_{70}S_{16}$ 123072-45-7, anticoagulant</td>
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<tr>
<td>arbutaminum arbutamine</td>
<td>arbutaminum arbutamine</td>
<td>(R)-3,4-dihydroxy-$\alpha$-[(4-(p-hydroxyphenyl)butyl]amino]methyl]benzyl alcohol</td>
<td>(R)-3,4-dihydroxy-$\alpha$-[(4-(p-hydroxyphenyl)butyl]amino]methyl]benzyl alcohol</td>
</tr>
<tr>
<td>arbutamine</td>
<td>arbutamine</td>
<td>$C_{18}H_{23}NO_{4}$ 128470-16-6, cardiac stimulant</td>
<td>$C_{18}H_{23}NO_{4}$ 128470-16-6, cardiac stimulant</td>
</tr>
<tr>
<td>avizafonum avizafone</td>
<td>avizafonum avizafone</td>
<td>2'-benzoyl-4'-chloro-2-[(S)-2,6-diaminohexamido]-N-methylacetanilide</td>
<td>2'-benzoyl-4'-chloro-2-[(S)-2,6-diaminohexamido]-N-methylacetanilide</td>
</tr>
<tr>
<td>avizafone</td>
<td>avizafone</td>
<td>$C_{22}H_{27}ClN_{4}O_{3}$ 65617-86-9, anxiolytic, anticonvulsant</td>
<td>$C_{22}H_{27}ClN_{4}O_{3}$ 65617-86-9, anxiolytic, anticonvulsant</td>
</tr>
<tr>
<td>barnidipinum barnidipine</td>
<td>barnidipinum barnidipine</td>
<td>(+)-(3'S,4S)-1-benzyl-3-pyrrolidinyl methyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate</td>
<td>(+)-(3'S,4S)-1-benzyl-3-pyrrolidinyl methyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate</td>
</tr>
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<tr>
<td>batelapinum</td>
<td>2-methyl-5-(4-methyl-1-piperazinyl)-11H-s-triazolo[1,5-c][1,3]benzodiazepine C_{16}H_{20}N_{6}</td>
<td>95634-82-5</td>
<td>antipsychotic</td>
</tr>
<tr>
<td>bemesetronum</td>
<td>endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl 3,5-dichlorobenzoate C_{15}H_{17}Cl_{2}NO_{2}</td>
<td>40796-97-2</td>
<td>serotonin antagonist</td>
</tr>
<tr>
<td>bertosamilum</td>
<td>3’-isobutyl-7’-isopropylspiro[cyclohexane-1,3’-[3,7]diazabicyclo[3.3.1]nonane] C_{19}H_{36}N_{2}</td>
<td>126825-36-3</td>
<td>anti-ischaemic</td>
</tr>
<tr>
<td>betamipronum</td>
<td>N-benzoyl-β-alanine C_{10}H_{11}NO_{3}</td>
<td>3440-28-6</td>
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<tr>
<td>bimakalimum</td>
<td>2,2-dimethyl-4-(2-oxo-1(2H)-pyridyl)-2H-1-benzopyran-6-carbonitrile C_{17}H_{16}N_{2}O_{2}</td>
<td>117545-11-6</td>
<td>potassium channel activator</td>
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<tr>
<td>Nonproprietary Name (Latin, English)</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
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<tr>
<td><strong>bindaritum</strong></td>
<td>2-[(1-benzyl-1H-indazol-3-yl)methoxy]-2-methylpropionic acid</td>
<td>antirheumatic</td>
<td></td>
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<tr>
<td>bindarit</td>
<td>C&lt;sub&gt;19&lt;/sub&gt;H&lt;sub&gt;20&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>130641-38-2</td>
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<tr>
<td><strong>brinazaronum</strong></td>
<td>p-[3-(tert-butylamino)propoxy]phenyl 2-isopropyl-3-indolizinyl ketone</td>
<td>calcium antagonist</td>
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<tr>
<td>brinazarone</td>
<td>C&lt;sub&gt;25&lt;/sub&gt;H&lt;sub&gt;32&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
<td>89622-90-2</td>
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<tr>
<td>carperitide</td>
<td>C&lt;sub&gt;127&lt;/sub&gt;H&lt;sub&gt;203&lt;/sub&gt;N&lt;sub&gt;45&lt;/sub&gt;O&lt;sub&gt;39&lt;/sub&gt;S&lt;sub&gt;3&lt;/sub&gt;</td>
<td>89213-87-6</td>
<td></td>
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<tr>
<td><strong>cefclidinum</strong></td>
<td>(+)-1-[(6R,7R)-7-[2-(5-amino-1,2,4-thiadiazol-3-yl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-3-yl methyl]-4-carbamoylquinucleidinium hydroxide, inner salt, 7&lt;sup&gt;2&lt;/sup&gt;-&lt;sup&gt;(Z)&lt;/sup&gt;-(O-methyloxime)</td>
<td>antibiotic</td>
<td></td>
</tr>
<tr>
<td>cefclidin</td>
<td>C&lt;sub&gt;27&lt;/sub&gt;H&lt;sub&gt;34&lt;/sub&gt;N&lt;sub&gt;6&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt;</td>
<td>105239-91-6</td>
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</table>
**Proposed International Chemical Name or Description, Molecular and Graphic Formulae**

**Nonproprietary Name (Latin, English)**

**Chemical Abstracts Service (CAS) registry number**

**Action and use**

**cefdaloximum**

**cefdaloxime**

\[(\pm)-(6R,7R)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, \(7\)\(^2\)-(Z)-oxime\]

\[C_{14}H_{15}N_5O_6S_2\]  
*antibiotic*

**ceronaprilum**

**ceronapril**

1-\{(2S)-6-amino-2-hydroxyhexanoyl\}-L-proline, hydrogen (4-phenylbutyl)phosphonate (ester)  
\[C_{21}H_{33}N_2O_6P\]  
111223-26-8  
*angiotensin converting enzyme inhibitor*

**cetrorelixum**

**cetrorelix**

\[N\text{-acetyl}-3\{-[2-naphthyl]-\text{o}-alanyl-\text{p}-\text{chloro-\text{o}}-\text{phenylalanyl}-3\{-[3-pyridyl]-\text{o}-alanyl-\text{\text{l}}\text{-seryl-\text{l}-tyrosyl-\text{N}_5\text{-carbamoyl-\text{d-ornithyl}}-\text{l-leucyl-\text{l}}-\text{arginyl-\text{l}}-\text{prolyl-\text{o}}-\text{alaninamide}}\]

\[C_{70}H_{92}CIN_17O_{14}S\]  
*antineoplastic*

**colfoscerili palmitas**

**colfosceril palmitate**

choline hydroxide, dihydrogen phosphate, inner salt, ester with \(\text{l-1,2-dipalmitin or 1,2-dipalmitoyl-sn-glycero-3-phosphocholine}\)

\[C_{40}H_{80}NO_8P\]  
63-89-8  
*surfactant replacement*

**corticorelinum**

**corticorelin**

corticotropin-releasing factor  
The source of the material should be indicated.  
\[C_{205}H_{339}N_{59}O_{63}S\]  
*diagnostic agent*
<table>
<thead>
<tr>
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<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>crospovidonum</td>
<td>1-vinyl-2-pyrrolidinone polymer, crosslinked</td>
<td>crospovidone</td>
<td>(C₆H₉NO)n 9003-39-8</td>
<td>pharmaceutical aid</td>
</tr>
<tr>
<td>dalteparinum natricum</td>
<td>Sodium salt of depolymerized heparin obtained by nitrous acid degradation of heparin from pork intestinal mucosa, the majority of the components have a 2-O-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-O-sulfo-2,5-anhydro-α-mannitol structure at the reducing end of their chain; the average relative molecular mass is about 5000, 90 per cent of which ranging between 2000 and 9000; the degree of sulfatation is 2 to 2,5 per disaccharidic unit.</td>
<td>dalteparin sodium</td>
<td>anticoagulant</td>
<td></td>
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<tr>
<td>dalvastatinum</td>
<td>(±)-(4R*,6S*)-6-[(E)-2-[2-(4-fluoro-m-tolyl)-4,4,6,6-tetramethyl-1-cyclohexen-1-yl]vinyl]tetrahydro-4-hydroxy-2H-pyrano-2-one</td>
<td>dalvastatin</td>
<td>C₂₄H₂₁FO₅ 132100-55-1</td>
<td>antihyperlipidaemic</td>
</tr>
<tr>
<td>dexormaplatinum</td>
<td>(+)-trans-tetrachloro(1,2-cyclohexanediamine)platinum</td>
<td>dexormaplatin</td>
<td>C₆H₄Cl₄N₂Pt 96392-96-0</td>
<td>antineoplastic</td>
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<tr>
<td>Chemical Name or Description, Molecular and Graphic Formulae</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
<td>Action and use</td>
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<tr>
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<td></td>
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<tr>
<td>didanosinum 2',3'-dideoxyinosine</td>
<td>C_{10}H_{12}N_{4}O_{3} 69655-05-6</td>
<td>antiviral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diethydtoluamidum N,N-diethyl-m-toluamide</td>
<td>C_{12}H_{17}NO 134-62-3</td>
<td>insect repellent</td>
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<tr>
<td>dofetilidum β-[N-methanesulfonamidophenyl)methylamino]methanesulfonyl-p-phenetidide</td>
<td>C_{19}H_{27}N_{3}O_{5}S_{2} 115256-11-6</td>
<td>antidysrhythmic</td>
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<tr>
<td>draflazinum (±)-4'-amino-4-[5,5-bis(p-fluorophenyl)pentyl]-2-carbamoyl-2',6'-dichloro-1-piperazineacetanilide</td>
<td>C_{28}H_{28}Cl_{5}F_{2}N_{5}O_{2} 120770-34-5</td>
<td>coronary vasodilator</td>
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<td></td>
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<tr>
<td>eberconazolum (±)-1-(2,4-dichloro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)imidazole</td>
<td>C_{18}H_{12}Cl_{2}N_{2} 128326-82-9</td>
<td>antifungal</td>
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<tr>
<td>Nonproprietary Name (Latin, English)</td>
<td>Chemical Name or Description, Molecular and Graphic Formulae</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
<td>Action and use</td>
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<tr>
<td>ecabetum</td>
<td>13-isopropyl-12-sulfopodocarpa-8,11,13-trien-15-oic acid</td>
<td>C_{20}H_{28}O_5S</td>
<td>antiulcer</td>
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<td>ecabet</td>
<td></td>
<td>33159-27-2</td>
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<td></td>
</tr>
</tbody>
</table>

![Diagram of ecabetum]

| englitazonum                      | (-)-5-([(2R)-2-benzyl-6-chromanyl]methyl]-2,4-thiazolidinedione | C_{20}H_{19}NO_3S                                 | antidiabetic  |
| englitazone                       |                                                           | 109229-58-5                                      |               |

![Diagram of englitazonum]

| enloplatinum                      | cis-(1,1-cyclobutanedicarboxylato)[tetrahydro-4H-pyran-4,4-bis(methylamine)]platinum | C_{13}H_{22}N_2O_5Pt                                | antineoplastic|
| enloplatin                        |                                                           | 111523-41-2                                      |               |

![Diagram of enloplatinum]

| eprobemidum                       | \(p\)-chloro-\(N\)-(3-morpholinopropyl)benzamide             | C_{14}H_{15}ClN_2O_2                                 | antidepressant|
| eprobemide                        |                                                           | 87940-60-1                                        |               |

![Diagram of eprobemidum]

| etarotenum                        | 6-[(\(E\)-\(p\)-(ethylsulfonyl)-\(\alpha\)-methylstyryl)-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene | C_{25}H_{32}O_2S                                    | dermatological|
| etarotene                         |                                                           | 87719-32-2                                        |               |

![Diagram of etarotenum]
<table>
<thead>
<tr>
<th>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>fadrozolum</td>
<td>(±)-p-(5,6,7,8-tetrahydroimidazo[1,5-a]pyridin-5-yl)benzonitrile C_{14}H_{13}N_{3}</td>
<td>102676-47-1</td>
</tr>
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<td>fantofaronum</td>
<td>1-[[p-[[3-[(3,4-dimethoxyphenethyl)methylamino]propoxy]phenyl]-sulfonyl]-2-isopropylindolizine C_{19}H_{38}N_{2}O_{5}S</td>
<td>114432-13-2</td>
</tr>
<tr>
<td>fasudium</td>
<td>hexahydro-1-(5-isoquinoysulfonyl)-1H,4-diazeapine C_{14}H_{17}N_{3}O_{2}S</td>
<td>103745-39-7</td>
</tr>
<tr>
<td>filgrastimum</td>
<td>N-L-methionylcolony-stimulating factor (human clone 1034) C_{845}H_{1339}N_{223}O_{243}S_{9}</td>
<td>121181-53-1</td>
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<tr>
<td>flosatidium</td>
<td>isobutyl [2-(dimethylamino)ethyl][[(o-(methylthio)phenyl)-[m-(trifluoromethyl)benzyl]carbamoyl]methyl]carbamate C_{26}H_{34}F_{3}N_{3}O_{3}S</td>
<td>113593-34-3</td>
</tr>
<tr>
<td>fluorodopum (18F)</td>
<td>3-(2-fluoro-18F-4,5-dihydroxyphenyl)-L-alanine C_{9}H_{10}^{18}FNO_{4}</td>
<td>92812-82-3</td>
</tr>
<tr>
<td>Proposed International</td>
<td>Chemical Name or Description, Molecular and Graphic Formulae</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
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<td>Nonproprietary Name (Latin, English)</td>
<td>Action and use</td>
<td></td>
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<tr>
<td>gadoteridolum</td>
<td>(±)-[10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclodecane-1,4,7-triacetato][3-]gadolinium</td>
<td>120066-54-8 paramagnetic contrast medium</td>
</tr>
<tr>
<td>gadoteridol</td>
<td>C_{17}H_{29}GdN_{4}O_{7}</td>
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</table>

| irinotecanum | (±)-7-ethyl-10-hydroxycamptothecine 10-[1,4'-biperidine]-1'-carboxylate or (±)-(S)-4,11-diethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]-quinoline-3,14(4H,12H)-dione 9-[1,4'-bipiperidine]-1'-carboxylate | 97682-44-5 antineoplastic |
| irinotecan | C_{33}H_{38}N_{4}O_{6} | |

| lanreotidum  | 3-(2-naphthyl)-o-alanyl-L-cysteinyll-L-tyrosyl-L-tryptophyl-L-lysyl-L-valyl-L-cysteinyll-L-threoninamide, cyclic (2→7)-disulfide | 108736-35-2 antineoplastic |
| lanreotide    | C_{54}H_{69}N_{11}O_{10}S_{2} | |

| lenograstim   | | |
leuciglumerum  
leuciglumer  
L-leucine polymer with 5-methyl hydrogen L-glutamate  
\((C_6H_{13}NO_2)_m \cdot (C_6H_{11}NO_4)_n\) 41385-14-2  
Dermatological

leurubicinum  
leurubicin  
(8S,10S)-10-[[3-[(S)-2-amino-4-methylvaleramido]-2,3,6-trideoxy-\(\alpha\)-L-/\(\beta\)-L]-lyxo-hexopyranosyl]oxy]-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione  
\(C_{33}H_{40}N_2O_{12}\) 70774-25-3  
Antineoplastic

levofloxacium  
levofloxacain  
(-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid  
\(C_{18}H_{20}FN_3O_4\) 100986-85-4  
Antibacterial

levomentholum  
levomenthol  
(-)-(1R,3R,4S)-menthol  
\(C_{10}H_{20}O\) 2216-51-5  
Decongestant, carminative
<table>
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<th><strong>Molecular and Graphic Formulae</strong></th>
<th><strong>Nonproprietary Name</strong> (Latin, English)</th>
<th><strong>Chemical Abstracts Service (CAS) registry number</strong></th>
<th><strong>Action and use</strong></th>
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</thead>
<tbody>
<tr>
<td>liarozolum</td>
<td>$(\pm)$-5-((m-chloro-α-imidazol-1-ylbenzyl)benzimidazole</td>
<td>liarozole</td>
<td>C$<em>{17}$H$</em>{13}$ClN$_4$ 115575-11-6</td>
<td>antiandrogen</td>
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<td><img src="image.png" alt="liarozolum formula" /></td>
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<tr>
<td>liranaftatum</td>
<td>$O$-(5,6,7,8-tetrahydro-2-naphthyl) 6-methoxy-N-methylthio-2-pyridinecarbamate</td>
<td>liranaftate</td>
<td>C$<em>{18}$H$</em>{20}$N$_2$O$_2$S 88678-31-3</td>
<td>antifungal</td>
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<td><img src="image.png" alt="liranaftatum formula" /></td>
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<tr>
<td>litoxetinum</td>
<td>4-(2-naphthylmethoxy)piperidine</td>
<td>litoxetine</td>
<td>C$<em>{16}$H$</em>{19}$NO 86811-09-8</td>
<td>antidepressant</td>
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<td><img src="image.png" alt="litoxetinum formula" /></td>
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<tr>
<td>loteprednolum</td>
<td>chloromethyl 11β,17-dihydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic acid</td>
<td>loteprednol</td>
<td>C$<em>{21}$H$</em>{26}$ClO$_5$ 129260-79-3</td>
<td>anti-inflammatory</td>
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<td><img src="image.png" alt="loteprednolum formula" /></td>
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<tr>
<td>loxoribinum</td>
<td>7-allyl-2-amino-9-β-D-ribofuranosylpurine-6,8(1H,9H)-dione</td>
<td>loxoribine</td>
<td>C$<em>{12}$H$</em>{15}$N$_2$O$_6$ 121288-39-9</td>
<td>immunostimulant</td>
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<td><img src="image.png" alt="loxoribinum formula" /></td>
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</table>
lufironilum
lufironil

\(N,N'\)-bis(2-methoxyethyl)-2,4-pyridinedicarboxamide
\(C_{13}H_{19}N_3O_4\) 128075-79-6 collagen inhibitor

mabuprofenum
mabuprofen

(\(\pm\))-\(N\)-(2-hydroxyethyl)-p-isobutylhydratropamide
\(C_{15}H_{23}NO_2\) 82821-47-4 analgesic, non-steroidal anti-inflammatory

melarsominum
melarsomine

bis[2-aminoethyl] \(p\)-[(4,6-diamino-s-triazin-2-yl)amino]dithiobenzene arsonite
\(C_{13}H_{21}AsN_8S_2\) 128470-15-5 antifilarial

minamestanum
minamestane

4-aminoandrosta-1,4,6-triene-3,17-dione
\(C_{19}H_{23}NO_2\) 105051-87-4 antineoplastic

mipragosidum
mipragoside

\(N-(\text{II}^3-N\text{-acetylneuraminosylgangliotetraosyl})\text{ceramide, isopropyl ester}\)
\(C_{76}H_{137}N_3O_{31}\) 131129-98-1 ganglioside
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<tr>
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<td>Action and use</td>
</tr>
<tr>
<td>mirfentanilum</td>
<td><strong>N</strong>-(1-phenethyl-4-piperidyl)-<strong>N</strong>-pyrazinyl-2-furamide</td>
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<tr>
<td>mirfentanil</td>
<td>C&lt;sub&gt;22&lt;/sub&gt;H&lt;sub&gt;24&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>117523-47-4</td>
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<td>mizolastinum</td>
<td>2-[[1-[1-(p-fluorobenzyl)-2-benzimidazolyl]-4-piperidyl[methylamino]-4(3H)-pyrimidinone</td>
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<tr>
<td>mizolastine</td>
<td>C&lt;sub&gt;24&lt;/sub&gt;H&lt;sub&gt;25&lt;/sub&gt;FN&lt;sub&gt;6&lt;/sub&gt;O</td>
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<td>108612-45-9</td>
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<tr>
<td>mofezolacum</td>
<td>3,4-bis(p-methoxyphenyl)-5-isoxazoleacetic acid</td>
</tr>
<tr>
<td>mofezolac</td>
<td>C&lt;sub&gt;19&lt;/sub&gt;H&lt;sub&gt;17&lt;/sub&gt;NO&lt;sub&gt;5&lt;/sub&gt;</td>
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<td>76967-07-4</td>
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<td>molgramostimum</td>
<td>colony-stimulating factor 2 (human clone pHG&lt;sub&gt;25&lt;/sub&gt; protein moiety reduced)</td>
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<td>molgramostim</td>
<td>C&lt;sub&gt;639&lt;/sub&gt;H&lt;sub&gt;1007&lt;/sub&gt;N&lt;sub&gt;171&lt;/sub&gt;O&lt;sub&gt;196&lt;/sub&gt;S&lt;sub&gt;8&lt;/sub&gt; (for protein moiety)</td>
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<td>99283-10-0</td>
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<td>mosapraminum</td>
<td>(±)-1'-[3-(3-chloro-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)propyl]hexahydrospiro[imidazo[1,2-a]pyridine-3(2H),4'-piperidin]-2-one</td>
</tr>
<tr>
<td>mosapramine</td>
<td>C&lt;sub&gt;28&lt;/sub&gt;H&lt;sub&gt;35&lt;/sub&gt;ClN&lt;sub&gt;4&lt;/sub&gt;O</td>
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<td>89419-40-9</td>
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nadifloxacinum
nadifloxacin

(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidino)-5-methyl-1-oxo-1H,5H-
benzo[1]quinoxaline-2-carboxylic acid
C_{19}H_{21}FN_{2}O_{4}  124858-35-1  antibacterial

nadroparinum calcium
nadroparin calcium

Calcium salt of depolymerized heparin obtained by nitrous acid degradation
of heparin from pork intestinal mucosa; the majority of the components
have a 2-O-sulfo-α-L-idopyranosuronic acid structure at the non-reducing
end and a 6-O-sulfo-2,5-anhydro-β-D-mannitol structure at the reducing end of
their chain; the average relative molecular mass is 4000 to 5000; the degree
of sulfatation is about 2.1 per disaccharidic unit.

anticoagulant

nafagrelum
nafagrel

(±)-5,6,7,8-tetrahydro-6-(imidazol-1-ylmethyl)-2-naphthoic acid
C_{15}H_{16}N_{2}O_{2}  97901-21-8  thromboxane A₂ synthetase
inhibitor

nafiracetamum
nafiracetam

2-oxo-1-pyrrolidineaceto-2',6'-xylidide
C_{14}H_{18}N_{2}O_{2}  77191-36-7  nootropic agent

nestifyllinum
nestifylline

7-(1,3-dithian-2-ylmethyl)theophylline
C_{11}H_{14}N_{4}O_{2}S_{2}  116763-36-1  antiasthmatic

ocaperidonum
ocaperidone

3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2,9-dimethyl-4H-
pyrido[1,2-a]pyrimidin-4-one
C_{24}H_{29}FN_{2}O_{2}  129029-23-8  antipsychotic
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<tr>
<td>oxiglutationum oxiglutationone</td>
<td>$N,N'$-[dithiobis([R]-1-[(carboxymethyl)carbamoyl]ethylene)]di-L-glutamine</td>
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<td>$C_{20}H_{32}N_6O_{12}S_2$ 27025-41-8</td>
</tr>
<tr>
<td>palonidipinum palonidine</td>
<td>$(\pm)$-3-(benzylmethylamino)-2,2-dimethylpropyl methyl 4-(2-fluoro-5-nitrophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate</td>
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<td>$C_{29}H_{34}FN_3O_6$ 96515-73-0 calcium antagonist</td>
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<td>panipenemum panipenem</td>
<td>$(\pm$)-(5R,6S)-3-[[S]-1-acetimidoyl-3-pyrrolidinyl]thio]-6-[(R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid</td>
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<td>$C_{15}H_{21}N_3O_4S$ 87726-17-8 antibiotic</td>
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<td>parnaparinum natrium parnaparin sodium</td>
<td>Sodium salt of depolymerized heparin obtained by hydrogen peroxide and cupric acetate degradation of heparin from pork intestinal mucosa; the majority of the components have a 2-O-sulfo-$\alpha$-L-idopyranosuronic acid structure at the non-reducing end and a 2-N,6-O-disulfo-$\alpha$-glucosamine structure at the reducing end of their chain; the average relative molecular mass is between 4000 and 6000 (5000 ± 10 per cent); the degree of sulfatation is 2.15 (± 10 per cent) per disaccharidic unit.</td>
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<td>anticoagulant</td>
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<tr>
<td>pegaspargasum pegaspargase</td>
<td>asparaginase, reaction product with succinic anhydride, esters with polyethylene glycol monomethyl ether</td>
</tr>
<tr>
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<td>130167-69-0 antineoplastic</td>
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<td>Chemical Name</td>
<td>International Name</td>
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<td>picumeterolum</td>
<td>picumeterol</td>
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<td>pirodomastum</td>
<td>pirodomast</td>
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<td>porfimerum natricum</td>
<td>porfimer sodium</td>
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<td>prinoxodanum</td>
<td>prinoxodan</td>
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quinotolastum
quinotolast
4-oxo-1-phenoxy-N-1H-tetrazol-5-yl-4H-quinolizine-3-carboxamide
C₁₇H₁₂N₄O₃  101193-40-2  antiallergic

quinupristinum
quinupristin
C₅₃H₆₇N₉O₁₀S  120138-50-3  antibacterial

racementholum
racemethol
(±)-(1R*,3R*,4S*)-menthol
C₁₀H₂₀O  15356-70-4  decongestant, carminative

regramostimimum
regramostim
colony-stimulating factor 2 (human clone pCSF-1 protein moiety reduced), glycoform GMC 89-107
C₆₃H₁₀₀N₁₇₁O₁₈₇S₈  127757-91-9  immunomodulator

reviparinum natrium
reviparin sodium
Sodium salt of depolymerized heparin obtained by nitrous acid degradation of heparin from pork intestinal mucosa; the majority of the components have a 2-O-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-O-sulfo-2,5-anhydro-α-mannitol structure at the reducing end of their chain; the average relative molecular mass is 3500 to 4500, 90 per cent of which ranging between 2000 and 8000; the degree of sulfatation is about 2.2 per disaccharidic unit.
  anticoagulant
ritolukastum
ritolukast
1,1,1-trifluoro-α-2-quinolylmethanesulfon-m-anisidide
C$_{17}$H$_{13}$F$_3$N$_2$O$_3$S 111974-60-8 antiasthmatic

sagandipinum
sagandipine
methyl (5-piperidinomethyl)furfuryl 4-(o-fluorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate
C$_{27}$H$_{31}$FN$_2$O$_5$ 126294-30-2 calcium antagonist

semotiadilum
semotiadil
( + )-(R)-2-[5-methoxy-2-[3-[methyl][2-[3,4-(methylenedioxy)phenoxy]ethyl]-amino]propoxy]phenyl]-4-methyl-2H-1,4-benzothiazin-3(4H)-one
C$_{29}$H$_{32}$N$_2$O$_6$S 116476-13-2 calcium antagonist

sorivudinum
sorivudine
( + )-1-β-D-arabinofuranosyl-5-[(E)-2-bromovinyl]uracil
C$_{11}$H$_{13}$BrN$_2$O$_6$ 77181-69-2 antiviral
<table>
<thead>
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<th>Chemical Name or Description</th>
<th>Molecular and Graphic Formulae</th>
<th>Action and Use</th>
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<tbody>
<tr>
<td>sumarotenum sumarotene</td>
<td>1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-[(E)-a-methyl-p-(methylsulfonyl)-styryl]naphthalene</td>
<td>dermatological</td>
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<td>C_{24}H_{30}O_{2}S</td>
<td>105687-93-2</td>
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<td>suplatastum tosilas</td>
<td>(±)[2-[[p-(3-ethoxy-2-hydroxypropoxy)phenyl]carbamoyl]ethyl]-dimethylsulfoxonium p-toluenesulfonate</td>
<td>anti-asthmatic, antiallergic</td>
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<tr>
<td>suplast tosilate</td>
<td>C_{23}H_{33}NO_{7}S_{2}</td>
<td>94055-78-2</td>
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<td>tamsulosinum tamsulosin</td>
<td>(−)-(R)-5-[2-[[2-(o-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide</td>
<td>α_{1}-adrenoreceptor antagonist</td>
</tr>
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<td>C_{20}H_{28}N_{2}O_{5}S</td>
<td>106133-20-4</td>
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<td>technetii (^{99m}Tc) bicisas</td>
<td>[N,N’-ethylenedi-L-cysteinato(3-)]oxo[^{99m}Tc] technetium(V), diethyl ester</td>
<td>radiocontrast medium</td>
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<td>technetium (^{99m}Tc) bicisate</td>
<td>C_{12}H_{21}N_{2}O_{5}S^{2+}^{99m}Tc</td>
<td>121281-41-2</td>
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<td>tematropii metilsulfas</td>
<td>3α-hydroxy-8-methyl-1αH,5αH-tropanium methyl sulfate (salt), (±)-ethyl hydrogen phenylmalonate</td>
<td>anticholinergic</td>
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<td>tematropium metilsulfate</td>
<td>C_{21}H_{31}NO_{8}S</td>
<td>113932-41-5</td>
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</tbody>
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208
temocaprilum
(+) \((2S,6R)-6-[[[(1S)-1-carboxy-3-phenylpropyl]amino]tetrahydro-5-oxo-2-(2-thienyl)-1,4-thiazepine-4(5H)-acetic acid, 6-ethyl ester
\( \text{C}_{22}\text{H}_{28}\text{N}_{2}\text{O}_{5}\text{S}_{2} \) 111902-57-9 angiotensin-converting enzyme inhibitor

terikalantum
(-)-1-[2-(4-chromanyl)ethyl]-4-(3,4-dimethoxyphenyl)piperidine
\( \text{C}_{24}\text{H}_{31}\text{NO}_{3} \) potassic channel blocker

vamicamidum
(\( \pm \)-\((\alpha\*)\)-\(\text{p-Chloro-phenyl} \)\( \alpha \)-\(\text{[\(\alpha\*)-2-(
\text{dimethylamino})propyl} \)\( \alpha \)-\(\text{Phenyl-2-pyridineacetamide} \)
\( \text{C}_{18}\text{H}_{23}\text{N}_{3}\text{O} \) 132373-81-0 anticholinergic, spasmolytic
vinfosiltinum  

[23(S)]-4-deacetyl-3-de(methoxycarbonyl)-3-[(2-methyl-1-phosphonopropyl)carbamoyl]vincaleukoblastine, diethyl ester  

$$C_{51}H_{72}N_5O_{10}P$$  

123286-00-0  

antineoplastic

---

vinleucinolium  

[23(1S,2S)]-4-deacetyl-3-[[1-carboxy-2-methylbutyl]carbamoyl]-3-(demethoxycarbonyl)vincaleukoblastine, ethyl ester  

$$C_{51}H_{69}N_5O_9$$  

antineoplastic

---

vorozolum  

(+)-6-(p-chloro-α-1H,1,2,4-triazol-1-ylbenzyl)-1-methyl-1H-benzotriazole  

$$C_{16}H_{13}ClN_6$$  

123731-10-8  

antineoplastic

---

zabiciprilatum  

(S)-2-[(S)-N-[(S)-1-carboxy-3-phenylpropyl]alanyl]-2-azabicyclo[2.2.2]octane-3-carboxylic acid  

$$C_{21}H_{28}N_2O_5$$  

90103-92-7  

antihypertensive
<table>
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<tr>
<th>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Nonproprietary Name (Latin, English)</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
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<td>zaltoprofenum</td>
<td>zaltoprofen</td>
<td>(±)-10,11-dihydro-α-methyl-10-oxodibenzo[b,f]thiepin-2-acetic acid</td>
<td>C₁₇H₁₄O₃S     89482-00-8</td>
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<td>zatosetronum</td>
<td>zatosetron</td>
<td>5-chloro-2,3-dihydro-2,2-dimethyl-N-1αH,5αH-tropan-3α-yl-7-benzofuran-carboxamide</td>
<td>C₁₉H₂₅ClN₂O₂  123482-22-4</td>
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<td>zenarestatum</td>
<td>zenarestat</td>
<td>3-(4-bromo-2-fluorobenzyl)-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazolineacetic acid</td>
<td>C₁₇H₁₁BrClFN₂O₄ 112733-06-9</td>
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<td>3,4-dihydro-4-oxo-3-[[5-(trifluoromethyl)-2-benzothiazolyl][methyl]-1-phthalazineacetic acid</td>
<td>C₁₉H₁₂F₃N₂O₅S 110703-94-1</td>
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Names for Radicals and Groups

Some substances for which a proposed international nonproprietary name has been established may be used in the form of salts or esters. The radicals or groups involved may be of complex composition and it is then inconvenient to refer to them in systematic chemical nomenclature. Consequently, shorter nonproprietary names for some radicals and groups have been devised or selected, and they are suggested for use with the proposed international nonproprietary names.

- **acistras**
  - acistrate
  - $2'$-acetate, stearate (salt)
  - $\text{C}_{20}\text{H}_{36}\text{O}_4$
  - ![ester](image)
  - ![salt](image)

- **etabonas**
  - etabonate
  - ethyl carbonate
  - $\text{C}_3\text{H}_6\text{O}_3$
  - ![ester](image)

- **pivotilum**
  - pivotil
  - 1-hydroxyethyl pivalate (ester)
  - $\text{C}_7\text{H}_{13}\text{O}_3$
  - ![ester](image)

- **triflutas**
  - triflurate
  - trifluoroacetate
  - $\text{C}_3\text{H}_5\text{F}_3\text{O}_2$
  - ![ester](image)
AMENDMENTS


Proposed International Nonproprietary Names (Prop. INN): List 1

p. 118 polyvidonum
polyvidone

replace the chemical name by the following:
1-vinyl-2-pyrrolidinone polymer, linear

WHO Chronicle, Vol. 24, No. 9, 1970

Proposed International Nonproprietary Names (Prop. INN): List 24

p. 433 fendizoatum
fendizoate

replace the chemical name, the CAS registry number and the graphic formula by the following:
2-[(6-hydroxybiphenyl-3-yl)carbonyl]benzoate
84627-04-3

Supplement to WHO Chronicle, Vol. 34, No. 9, 1980

Proposed International Nonproprietary Names (Prop. INN): List 44

p. 15 loprazolamum
loprazolam

replace the chemical name and the CAS registry number by the following:
(Z)-6-(o-chlorophenyl)-2,4-dihydro-2-[(4-methyl-1-piperazinyl)methylene]-8-nitro-1H-imidazo[1,2-a][1,4]benzodiazepin-1-one
70111-54-5

Supplement to WHO Chronicle, Vol. 38, No. 4, 1984

Proposed International Nonproprietary Names (Prop. INN): List 52

p. 9 enoxaparinum
enoxaparin

delete the whole entry

Sodium salt of depolymerized heparin obtained by alcaline degradation of heparin benzyl ester from pork intestinal mucosa; the majority of the components present a 2-O-sulfo-4-enepyranosuronic acid structure at the non-reducing end and a 2-N,6-O-disulfo-o-glucosamine structure at the reducing end of their chain; the average relative molecular mass is about 4500, ranging between 3500 and 5500; the degree of sulfatation is about 2 per disaccharidic unit.

anticoagulant
Proposed International Nonproprietary Names (Prop. INN): List 55

p. 17  efrotomycinum  efrotomycin

replace the chemical name, and the graphic formula by the following:
an antibiotic produced by *Streptomyces lactamdurans* efrotomycin A, or
\((uS,2R,3R,4R,6S)-4-[(6-deoxy-4-O-(6-deoxy-2,4-di-O-methyl-\(\alpha\)-L-mannopyranosyl))-3-O-methyl-\(\beta\)-\(\alpha\)-allopyranosyl)oxy]-N\([2(E)4E,6S,7R]-7\:[(2S,3S,4R,5R)-5-[(1E,3E,5E)-6-(1,2-dihydro-4-hydroxy-1-methyl-2-oxonicotinoyl)-1,3,5-heptatrienyl]tetrahydro-3,4-dihydroxy-2-furyl]-6-methoxy-5-methyl-2,4-octadienyl]-\(\alpha\)-ethyltetrahydro-2,3-dihydroxy-5,5-dimethyl-6-[(1E,3Z)-1,3-pentadienyl]-2H-pyran-2-acetamide


Proposed International Nonproprietary Names (Prop. INN): List 58

p. 182  delete  insert
levdropropizinum  levdropropizinum
levdropropizine  levdropropizine

WHO Drug Information, Vol. 2, No. 4, 1988

Proposed International Nonproprietary Names (Prop. INN): List 60

p. 2  acemannanum  acemannan

delete the graphic formula and replace the description by the following:
Acemannan is a highly acetylated, polydispersed, linear mannan obtained from the mucilage of *Aloe barbadensis*, Miller (aloevera).


Proposed International Nonproprietary Names (Prop. INN): List 61

p. 14  moxidectinum  moxidectin

replace the chemical name by the following:

p. 17  delete  insert
taludipinum  teludipinum
taludipine  teludipine

214
Proposed International Nonproprietary Names (Prop. INN): List 62

p. 8  fosquidonum  
fosquidone

replace the chemical name by the following:

Proposed International Nonproprietary Names (Prop. INN): List 63

p. 5  doramectinum  
doramectin

replace the chemical name by the following:
25-cyclohexyl-5-O-demethyl-25-de(1-methylpropyl)avermectin A₁₈ or (2aE,4E,8E)-5'S,6'S,6'R,7'S,11'R,13'S,15'S,17αR,20R,20αR,20βS)-6'-cyclohexyl-5'·6'·7·10·11·14·15·17α·20·20α·20β-dodecahydro-20·20β-di hydroxy-5'·6·8·19-tetramethyl-17-oxospiro[11,15-methano-2H,13H,17H-furo-[4,3,2-pq][2,6]benzodioxacyclooctadecin-13,2'-[2H]pyran]-7-yl 2,6-dideoxy-4-0-(2,6-dideoxy-3-O-methyl-α-L-arabino-hexopyranosyl)-3-O-methyl-α-L-arabino-hexopyranoside

p. 6  giracodazolum  
giracodazole

replace the chemical name by the following:
(a$)$-2-amino-α-[(1S)-2-amino-1-chloroethyl]imidazole-4-methanol

p. 8  nemazolinum  
nemazoline

insert the following CAS registry number:
130759-56-7

neticonazolum  
neticonazole

replace the CAS registry number by the following:
130726-68-0

p. 14  tenosiprolum  
tenosiprol

insert the following CAS registry number:
129336-81-8

p. 16  zilascorbum (¹H)  
zilascorb (¹H)

replace the chemical name by the following:
5,6-O-[(RS)-benzylidene-α-d]-l-ascorbic acid

Procedure and Guiding Principles

The text of the Procedures for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances and General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances will from now on be reproduced in uneven numbers of proposed INN lists only.
**SELECTED WHO PUBLICATIONS OF RELATED INTEREST**

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<tr>
<th>Title</th>
<th>Price* (Sw. fr.)</th>
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<td><strong>The use of essential drugs</strong></td>
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<tr>
<td>Fourth report of the WHO Expert Committee</td>
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<tr>
<td>WHO Technical Report Series, No. 796</td>
<td>8.– (5.60)</td>
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<tr>
<td>1990 (57 pages)</td>
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<tr>
<td><strong>Guidelines for developing national drug policies</strong></td>
<td></td>
</tr>
<tr>
<td>1988 (iv + 52 pages)</td>
<td>11.– (7.70)</td>
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<tr>
<td><strong>The International Pharmacopoeia, third edition</strong></td>
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<tr>
<td>Volume 1: general methods of analysis. 1979 (223 pages)</td>
<td>24.– (16.80)</td>
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<td>36.– (25.20)</td>
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<tr>
<td>Volume 3: quality specifications. 1988 (407 pages)</td>
<td>64.– (44.80)</td>
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<tr>
<td><strong>International Nonproprietary Names (INN) for pharmaceutical substances, cumulative list no. 7</strong></td>
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<tr>
<td>1988 (xviii + 617 pages)</td>
<td>65.– (45.50)</td>
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<td><strong>Basic tests for pharmaceutical substances</strong></td>
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<tr>
<td>1986 (vi + 204 pages)</td>
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* Prices in parentheses apply in developing countries.

Further information on these and other World Health Organization publications can be obtained from Distribution and Sales, World Health Organization, 1211 Geneva 27, Switzerland.