



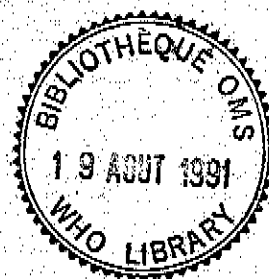
# WHO

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## THIRD CONSULTATION ON SYSTEMS OF CLASSIFICATION FOR PHARMACEUTICALS AND FOR DEFINED DAILY DOSES

Report on a WHO Consultation



Oslo  
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## TARGET 31

### ENSURING THE QUALITY OF SERVICES

#### Index terms

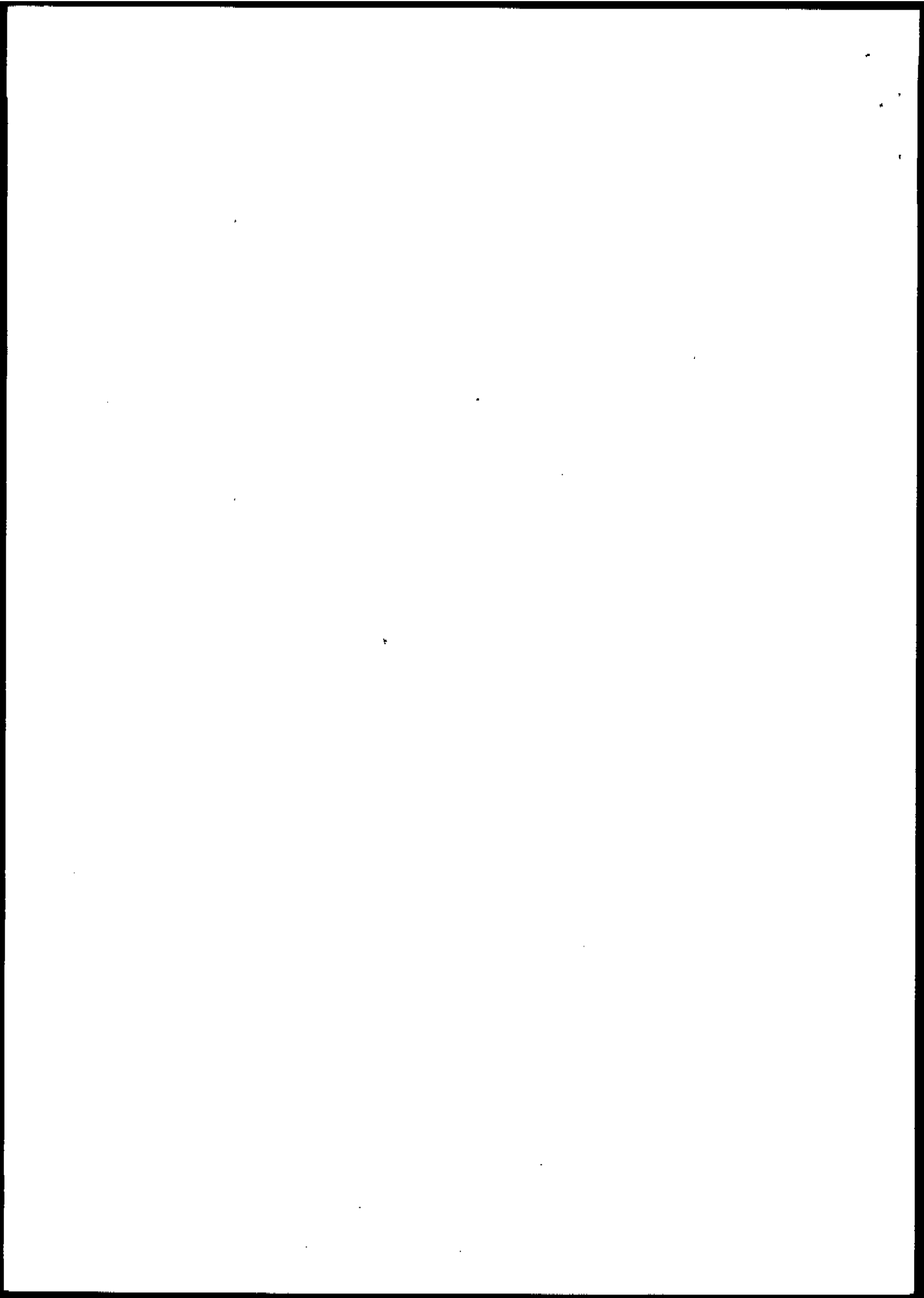
DRUGS - classification  
DRUGS - administration and dosage  
NET

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<sup>a</sup> *Targets for health for all. Copenhagen, WHO Regional Office Europe, 1985 (European Health for All Series, No. 1).*

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## 1. Introduction

This meeting was the third in a series of consultations on the use of the ATC/DDD system for cost-containment measures.

The first of these consultations was held in Copenhagen on 5-6 October 1989 and the second took place in Oslo on 14 December 1990.

The aim of the third consultation was to:

- . identify similarities and differences between the ATC classification system and the Dutch Medicines Reimbursement System (MRS);
- . decide on recommendations for the use of the ATC system for cost containment measures;
- . identify differences between the DDDs established by the WHO Collaborating Centre (WHO CC) and the DDDs used by the MRS;
- . decide on recommendations for the use of DDDs for cost containment measures;
- . plan for the further development of the ATD/DDD system and the MRS.

## 2. Developments since the previous consultation

Dr K. Oydvin, WHO Collaborating Centre, Oslo, informed the meeting about the steps that had been taken to increase the acceptance and use of the ATC/DDD system.

### WHO, Geneva

A small consultation was held on 24 February 1991 in WHO Headquarters (WHO/HQ), Geneva, between representatives from the Action Programme for Essential Drugs and the Pharmaceuticals Programme in Geneva, Dr Oydvin, and Ms I. Lunde from WHO Regional Office for Europe (WHO/EURO), Copenhagen. During the consultation the representatives from WHO/HQ presented their requirements to a drug classification system. They also described the problems that they would be faced with if they were to use the ATC system.

It was decided that Dr Oydvin would prepare a document which would describe how the requirements described by WHO, Geneva, could met and how problems could be overcome.

Another consultation would then be arranged to discuss this document in more detail.

### IMS

A meeting will be held on 11-13 September 1991 with representatives from the IMS and the WHO CC to discuss how the WPhMRA-system and the ATC-system can be harmonized.

### European Economic Community (EEC)

Ms Lunde met Mr F. Sauer and his colleagues in Brussels 21 February 1991 to discuss the use of the ATC system by the EEC. It seems likely that the EEC will adopt the ATC-system as their common system for classification of drugs.

The WHO CC will be invited to participate in some of the meeting of the EEC Working Groups to explain the system in more detail.

### 3. Similarities and differences between the ATC classification system and the Dutch Medicines Reimbursement System (MRS)

Dr C. M. de Vos gave a brief outline of the Dutch MRS (Annex 1).

### Discussion

#### Interchangeability

When deciding on the drugs that can be regarded as "interchangeable", newly introduced drugs may represent a problem since the knowledge of their adverse drug reactions will be limited at that time. There are also many examples of drugs for which the main indication has been changed after the drug has come into general use.

The ATC-system, which can be regarded as a relatively static system, cannot always reflect these type of changes and therefore this system cannot ensure "interchangeability" in all cases.

#### Classification of drugs that do not belong in already established ATC-groups

When classifying drugs according to the ATC-system, the practice up until now has been to put new substances which do not belong in an already existing group, into the X-group. (If the new drug has a clearly defined and new mode of action, a new 4th level may however be established.)

The X-group, therefore, usually is very inhomogenous, containing many different therapeutic groups. This might create a problem for the Dutch classification which aims at achieving interchangeability.

It was agreed that the WHO CC would pay more attention to this when classifying new substances or revising already existing classifications.

It was also agreed that the WHO CC would revise existing X-groups, starting with the more important ones.

#### Classification of drugs with different adverse drug reactions (ADRs)

Differences in ADRs will normally not be reflected in the ATC-classification but can be introduced in any additional classification such as it is done in the MRS.

### Classification of drugs with different strengths or routes of administration

If differences in dosage presentation means differences in therapeutic effect and/or ADRs then this difference will be reflected in the classification. Such differences are only reflected in the ATC-system if the different dosage forms or strength of one particular drug are used for clearly different indications.

Differences in strengths and routes of administration will not normally be reflected in the ATC-classification but can be introduced in any additional classification such as it is done in the MRS.

It was recommended that a clear explanation about the principles used by the MRS when classifying different dosage forms and strengths should be included in the explanatory guidelines to the MRS.

### Examples of differences between the MRS and the ATC classification

Specific examples of drug substances and drug groups where the MRS differs from the ATC classification were presented.

The examples are presented in Annex 2. The discussion and the decisions taken are reported in Annex 3.

### How can the ATC classification system and the MRC be improved?

The participants from The Netherlands said that they had no problems with using the present ATC-system in their MRS classification. Their main concern was to ensure that the ATC-system would be continuously updated so that it would reflect new developments.

It was recommended that the ATC-classification system should be seen as a "core" classification which, in principle, would be relatively static. More detailed codes could then be added to the "core" classification to make the system more suitable for specific purposes such as cost containment. This additional coding may be more dynamic and easy to change.

The WHO CC is at present establishing a new working-group for drug classification. It was decided that the terms of reference for this working-group would be commented upon by the Netherlands to ensure that their views and interests were properly reflected.

#### 4. Recommendations for the use of the ATC-system for cost-containment measures

Before recommending the use of the ATC-system for cost-containment measures, the principles for such use should be defined and guidelines for extending the ATC-code should be prepared.

In addition, some practical results of using the system for this purpose should be available.

Action: The Netherlands will prepare a description of the aim of the MRS and this will be presented during the WHO DURG-meeting in Verona together with an outline of the system.

When the system has been tried out and the results have been evaluated then it may be introduced into the "Guidelines for use of the ATC-system".

5. Differences between the DDDs established by the WHO CC and the DDDs used in the MRS

The DDDs established by the WHO CC are basically linked to substances whereas in The Netherlands they are linked to pharmaceutical preparations.

The participants from The Netherlands presented some examples of drug substances where the MRS-classification differed from the principles underlying the DDDs established by the WHO CC.

Beta-2-agonists

The DDDs for aerosols and powder formulations are the same in the ATC-system even if the recommended therapeutic dose of the powder is twice as high as the dose for aerosols.

The DDDs for asthma aerosols and powder for inhalation will be reconsidered by the WHO CC.

Calciumantagonists

The participants from The Netherlands felt that the DDDs within this group were not comparable e.g. the DDD for verapamil was higher than the recommended therapeutic dose whereas the the DDD for nifedipine was lower etc.

The WHO CC informed the meeting that they were trying to achieve equipotent DDDs within each therapeutic group. In this particular group verapamil was the reference substance. In general, the DDDs were kept in the lower range of the recommended dose within this group, since the dosing within this group generally can be expected to decrease.

The recommended therapeutic doses may, however, vary from country to country and this may help to explain why some countries may not find that the DDDs are equipotent.

Action: It was decided that The Netherlands would prepare the documentation for which they felt the DDDs were not equipotent within this group and send this information to the WHO CC for consideration.

It was furthermore recommended that the introduction to the MRS classification should point to the fact that although the established DDDs have been used as the starting point, it is the Dutch standard doses that have been used as a basis for the MRS classification.

Neuroleptics

Established DDDs have been used in the MRS classification except for Sulpiride where The Netherlands felt the DDD was too high.

Action: The WHO CC will inform The Netherlands about the background for the DDD for sulpiride.

It was concluded that differences in DDDs are difficult to avoid since there will always be national differences in the recommended therapeutic dose for some substances.

Errors, however, will be corrected if satisfactory documentation for the change needed is presented to the CC.

**Action:** The Netherlands will prepare a list of proposals for changes that they feel are necessary with the required documentation and send it to the WHO CC for consideration. Priorities should be indicated in the proposal.

6. Recommendations for use of DDDs for cost containment measures

- . The use of DDDs for cost containment purposes should be encouraged and the DDD system should, as far as possible, be adapted to make it suitable also for this purpose.
- . Guidelines describing the use of DDDs for cost containment measures should describe advantages as well as limitations of such use.

**Action:** The Netherlands will prepare a draft proposal for the use of DDDs for cost-containment purposes.

The proposal should be sent to the WHO CC in Oslo before 20 May 1991. It will then be considered by the Working Group.

7. Further development of the ATC/DDD and the MRS-system.

After the MRS system has been tried out in The Netherlands and some experience has been gained, they will prepare a proposal for how the use of the ATC/DDD-system, for cost-containment purposes, should be formulated in the official recommendations for the use of the system. This proposal will be considered by the WHO-CC Advisory Board before it is published in the official recommendations for the use of the ATC/DDD system.

When the use of the ATC/DDD system for cost-containment purposes has been included in the official recommendations, a separate working group which will deal with cost-containment questions, will be established

OSLO, April 23rd 1991

dr. C.M. de Vos

I would like to give a brief outline of the Dutch medicines reimbursement system. I think that this will in particular be useful for those not present last time for understanding the system and I think that for the other persons present at this meeting it will be a useful refreshers course.

The central problem of pharmaceutical care in the Netherlands is that the costs are too high and that especially the growth of the costs should be contained. We think that for the Netherlands a yearly growth of the costs of pharmaceutical care of about four percent is acceptable.

This is still two percent more than is allowed for the growth of the total health care.

We perceived that not the supply-side - the manufacturers of drugs - are to be blamed for the cost increase, because they are acting in an economically sensible way. Their objective is to make optimal use of the available environmental factors and to make as much profit as possible.

This is an accepted behaviour in our society.

In our opinion the real problem can be found at the demand-side.

The demand-side existing of physicians, patients, sickfunds and insurance-companies.

Physicians do not consider the costs of drugs as a significant criterion for choosing drugs. They conceive drugs only as an instrument to satisfy the needs of the patients and they prove to be susceptible to the marketing efforts of the pharmaceutical industry.

New drugs come into the market at, in general, higher prices than the older drugs in the same pharmacotherapeutical class and doctors tend to replace older drugs by newer drugs. Many of these new drugs increase the costs of pharmaceutical care unnecessarily, because they are no real innovations, but variations on the same theme, which provide no added value.

As far as patients are concerned: they do not pay the drugs directly and therefore do not ask for cheaper drugs.

Insurance companies and sickfunds are not capable to negotiate with pharmaceutical companies and they react to cost increase by raising the premiums that are payed to them by the patients.

What we need in the Netherlands is a reimbursement system that urges the demandside, the doctors and patients, to be cost conscious.

We need a system that compels them to ask for cheaper drugs.

Limiting conditions for such a system are:

first: it is necessary that the quality of pharmacotherapy will be preserved;

secondly: co-payment is not politically acceptable in the Netherlands. Therefore it must be possible to avoid co-payment.

The Dutch medicines reimbursement system is based on the assumption that drugs can be divided into groups of interchangeable drugs.

If one succeeds in creating such groups of interchangeable drugs, each drug of the group can be replaced by the other and no necessity exists to reimburse drugs out of the group above a set cost limit, because good pharmacotherapy is possible with all drugs within the group, especially also with those below the cost limit.

Therefore, physicians can choose drugs out of such a group of interchangeable drugs with a price below the cost limit. The patient will receive good therapy without co-payment. He gets qualitatively good treatment at limited costs and everybody is satisfied except for some pharmaceutical industries.

The core of the system is that within the groups of interchangeable drugs a limit is established. New drugs can enter the groups of interchangeable drugs but are confronted with a fixed limit. Therefore the replacement of older with newer equivalent drugs will occur at a lower price-level.

To give an example: if a price limit would have been fixed in 1987 in the group of the H<sub>2</sub>-antihistamine receptor antagonists at the level of Tagamet, between 1987 and 1989, we would have saved about sixty million Dutch guilders.

The hot topic in introductions last and this year in the Netherlands are the calcium antagonists. Some of them have been introduced at very high prices. The medicines reimbursement system would have saved us to a great extent unnecessary cost increase.

We have developed the system since early 1988.

In 1989 we submitted a first draft of the medicines reimbursement system to a panel of top level clinicians, each of them specialists on pharmacotherapy in their own respective fields. These consultations resulted in further refinements of the grouping of drugs. In the spring of 1990 the system was ready for publication.

It was published last year May in the Dutch Official Gazette and sent to the representative organisations and separately to all pharmaceutical companies active in our country and to all physicians and pharmaceutical practitioners.

Their technical comments were analyzed and where appropriate incorporated into the system. This resulted in the second concept of the medicines reimbursement system, which was sent to Parliament in November 1990.

This second concept was the one we discussed in our meeting of December last year.

Parliament said yes to the system on the seventeenth of December.

The secretary of health promised that the second concept of the reimbursement system would be sent for final screening to a Committee of the Dutch Sick Fund Council, especially established for this system.

This committee is called the Committee Reimbursement Limits of Medicines and consists of independent medical and pharmaceutical experts.

The committee was asked to advise with regard to the criteria for grouping drugs and establishing standard doses.

Furthermore the committee was asked to review the groups of interchangeable drugs and to consider whether the classification of the groups was according to the criteria for grouping drugs.

I now want to repeat the criteria for making up groups of interchangeable drugs, which I discussed during our meeting in December.

I stated: drugs are considered to be interchangeable provided that

- a) they have the same or comparable main mode of action and are applicable in the same or comparable main indications;
- b) there are no therapeutically relevant differences between the side-effects of the products according to the Pharmaceutical Compass of the Central Medical Pharmaceutical Commission of the Dutch Sick Fund Council;
- c) they are used in the same way of administration, with the presumption that for the purpose of classification into groups the oral, oromucosal and transdermal way of administration are considered to be identical ways of administration;
- d) they are generally intended for the same age group.

According to the advice of this committee the criteria were rephrased to some extent.

The principal change of the criteria is the rephrasing of the criterion on side-effects.

This criterion now reads: not having clinically relevant differences in desirable and non-desirable properties.

This means there should be a professional consensus with concern to the properties of medicines.

Furthermore the words 'main indications' are replaced by the words 'similar area of possible usage' and the words 'main mode of action' by the words 'similar mode of action or mechanism of action'.

This rephrasing of the criteria did not change the essentials of the Dutch medicines reimbursement classification. The rephrasing was principally meant as a clarification of the criteria themselves.

Some groups of interchangeable medicines were revised because the committee thought that these groups were not made up in accordance with the criteria. All technical propositions and amendments of the committee were adopted. This means that the criteria were changed in the way as mentioned before and that the groups of interchangeable drugs were changed in accordance with the propositions of the committee.

Both these rounds of consultation last year brought about a huge stream of reactions from the side of the pharmaceutical industry. These letters were carefully screened by the committee and incorporated in its advice.

The committee has a permanent status and will advise in future with regard to the grouping of all new drug introductions and with regard to the standard doses of these new drugs.

The rule on the medicines reimbursement system has been signed by the secretary of health and was published in the Official Gazette of last April the sixteenth. The rule will become effective on the first of July next. So far the history of the medicines reimbursement system.

The development of the medicines reimbursement system showed us that such a system is only acceptable in the Netherlands, provided that the grouping of drugs satisfies all criteria of interchangeability. Drugs in such groups must have the same mode of action and indications and must not have therapeutically relevant differences.

In the first place the medicines reimbursement system classification is a therapeutical one which reflects the current state of the art. Therefore the primary role of the Committee Reimbursement Limits of Medicines is to monitor the grouping of drugs and to make sure that this reflects the state of the art.

The medicines reimbursement system is a dynamic system. The ATC-classification is more static because to keep the ATC-classification stable during a longer period, it is thought to be desirable for longitudinal drug research studies. The same holds true for the DDD-system.

The purpose of our meeting today and tomorrow is to discuss how national classifications like the Dutch medicines reimbursement system can be made compatible with the ATC-classification.

Furthermore, I think it should be discussed whether a standard dose system should or could be more dynamic too.

Besides, I think we should discuss whether defined daily doses should more reflect equipotencies within groups. The standard doses of drugs in groups should be brought more into relation with each other. However, this is only possible when the drugs in the groups are really interchangeable.

Considerations on splitting the ATC-group A02BX  
(other drugs for the treatment of peptic ulcer).

This group is represented by:

- A02BX02; Sucralfate
- A02BX03; Pirenzepine
- A02BX05; Bismuth subcitrate

The ATC-group has been split into the separate substances.

0A02BXB0 V with  
A02BX02; Sucralfate

0A02BXC0 V with  
A02BX03; Pirenzepine

0A02BXD0 V with  
A02BX05; Bismuth subcitrate

The rationale for the division of the A02BX ATC-group is based on differences in mode of action.

Sucralfate acts as a mucoprotective agent by providing a physical protective barrier with regard to the gastric mucosa.

Pirenzepine is a selective antimuscarine agent which causes a reduction in the secretion of gastric acid. It also reduces the secretion of pepsin.

Bismuth subcitrate not only has a mucosal protective mode of action but has been shown to act bactericidal to the *Campylobacter pyloridis* too.

Considerations on splitting the ATC-group A07DA  
(antipropulsives).

This group is represented by:  
A07DA01; Diphenoxylate  
A07DA03; Loperamide

The ATC-group has been split into the separate substances.

0A07DAB0 V with  
A07DA01; Diphenoxylate

0A07DAC0 V with  
A07DA03; Loperamide

The rationale for the division of the A07DA ATC-group is based on differences concerning the adverse effects of the two substances.

The chemical structure of diphenoxylate has great resemblance to pethidine however it has no analgetic properties. Once absorbed, it causes central nervous system adverse effects. Loperamide is a much safer agent in this respect. It does not have adverse effects on the central nervous system.

Considerations on splitting the ATC-group A07EC (aminosalicylic acid).

This group is represented by:

A07EC01; Sulphasalazine

A07EC02; Mesalazine

A07EC03; Olsalazine

The ATC-group has been split into five groups.

0A07ECB0 V with

A07EC01; Sulphasalazine

0A07ECC0 V with

A07EC02; Mesalazine

A07EC03; Olsalazine

0A07ECBR QV (rectal preparations) with

A07EC01; Sulphasalazine

0A07ECCR QV (rectal preparations) with

A07EC02; Mesalazine

0A07ECCRC V (rectal preparations) with

A07EC02; Mesalazine

The rationale for the division of the A07EC ATC-group is based on differences concerning the adverse effects of the three substances.

The pharmacological active substance mesalazine is a metabolite of sulphasalazine and olsalazine through bacterial degradation in the colon.

Orally administered sulphasalazine has adverse effects which the other two substances do not have. This is caused by sulphapyridine; a metabolite of sulphasalazine. The rectal preparations of mesalazine and sulphasalazine are furthermore divided, for the rectal preparation of sulphasalazine is not active because the active metabolite, mesalazine, is not formed in the rectum.

Considerations on splitting the ATC-group A08AA  
(centrally acting antiobesity products).

This group is represented by:  
A08AA02; Fenfluramine  
A08AA04; Dexfenfluramine  
A08AA05; Mazindol

The ATC-group has been split into two groups

**0A08AAB0 V** with  
A08AA02; Fenfluramine  
A08AA04; Dexfenfluramine

**0A08AAC0 V** with  
A08AA05; Mazindol

The rationale for the division of the A08AA ATC-group is based on differences in the mode of action of the two groups. Fenfluramine and dexfenfluramine are serotonin antagonists. Mazindol is an indirect acting sympathicomimetic agent with  $\alpha$ - and  $\beta$ -adrenergic activity.

Considerations on splitting the ATC-group C01DA  
(anti-anginal vasodilators).

This group is represented by:

- C01DA01; Dipyridamole — Has been moved.
- C01DA02; Nitroglycerin
- C01DA08; Isosorbide dinitrate
- C01DA14; Isosorbide mononitrate
- C01DA05; Pentaeritryl tetranitrate

The ATC-group has been split into four groups

OC01DAB0 V with  
C01DA01; Dipyridamole

OC01DAC0 V with  
C01DA02; Nitroglycerin  
C01DA08; Isosorbide dinitrate  
C01DA14; Isosorbide mononitrate  
C01DA05; Pentaeritryl tetranitrate

OC01DAD0 V with  
C01DA02; Nitroglycerin  
C01DA08; Isosorbide dinitrate

OC01DAE0 QV with  
C01DA11; Oxymetazoline

The rationale for the division of the C01DA ATC-group is based in the first place on the consideration whether the nitrates are used in the treatment of the acute attack of angina pectoris or whether they are used in the prevention of angina pectoris. In the second place, a distinction has been made in the mode of action of the three different chemical classes that occur in the ATC-group.

The OC01DAD0 V group contains the presentations which are used in the treatment of acute attacks of angina pectoris. The OC01DAC0 V group contains the presentations which are used in maintenance therapy.

Oxymetazoline is a partial agonist of  $\beta$ -adrenoceptors.

The mode of action of oxymetazoline is different from the nitrates which are thought to have only a vasodilatory action on the smooth muscle tissue. Therefore oxymetazoline has been put into the group OC01DAE0 QV.

The mode of action and the indications of dipyridamole are very different from the other substances in the ATC-group. It has antithrombotic activity and is used in conditions where modification of platelet function may be beneficial. Therefore dipyridamole has been put into the group OC01DAB0 V.

Considerations on splitting the ATC-group C02DE (calcium channel blockers).

This group is represented by:

C02DE01; Verapamil  
C02DE02; Nifedipine  
C02DE04; Diltiazem  
C02DE05; Nitrendipine  
C02DE09; Nicardipine  
C02DE10; Felodipine  
C02DE03; Nimodipine  
C02DE07; Lidoflazine

This ATC-group has been split into four groups.

OC02DEB0 V with  
C02DE01; Verapamil

OC02DEC0 V with  
C02DE02; Nifedipine  
C02DE04; Diltiazem  
C02DE05; Nitrendipine  
C02DE09; Nicardipine  
C02DE10; Felodipine

OC02DED0 V with  
C02DE03; Nimodipine

OC02DEE0 QV with  
C02DE07; Lidoflazine

The rationale for the division of the C02DE ATC-group is based on differences in the mode of action or/and in indications. With regard to the mode of action, it has been established that the effects of the individual agents are being modified by their selectivity of action at different tissue sites. The main action of nifedipine, nitrendipine, nicardipine and felodipine is peripheral vasodilation and with some of these agents coronary vasodilation takes place, resulting in reduced bloodpressure and increased coronary bloodflow. Diltiazem is somewhat different from the other substances in this group. Its range of actions is more comparable with that of verapamil. The fact that diltiazem has greater vasodilator properties than verapamil and that its clinical use is restricted to angina pectoris and hypertension, is the reason for putting diltiazem into the current group and not into the group with verapamil. Verapamil, has a wider mode of action than the substances classified in the OC02DEC0 V group. It is primarily used as an antiarrhythmic although it is used in angina and hypertension too. Nimodipine, is primarily used for its cerebral vasodilatory effect. For this reason it has been placed into in a separate group. Finally lidoflazine is a calcium overload blocker as opposed to nifedipine, nitrendipine, nicardipine and felodipine which are calcium entry blockers.

Considerations on splitting the ATC-group C04AX  
(other peripheral vasodilators).

This group is represented by:

C04AX01; Cyclandelate  
C04AX06; Betahistine  
C04AX22; Flunarizine  
C04AX ; Buflomedil hydrochloride

The ATC-group has been split into the separate substances.

OC04AXB0 V with  
C04AX01; Cyclandelate

OC04AXD0 V with  
C04AX06; Betahistine

OC04AXE0 V with  
C04AX22; Flunarizine

OC04AXF0 Q V with  
C04AX ; Buflomedil hydrochloride

The rationale for the division of the C04AX ATC-group is based on the differences in modes of action and the concomitant differences in indications.

It has been established that cyclandelate inhibits phosphodiesterase and aldose reductase. The substance has been shown to cause preservation of erythrocyte deformability, inhibition of platelet aggregation, inhibition of atherosclerosis and inhibition of endogenous cholesterol synthesis. It is used in the treatment of cerebrovascular and peripheral vascular disorders.

Betahistine is a histamine analogue and is claimed to improve the microcirculation. It is used to reduce the symptoms of Ménières disease.

Flunarizine is the difluorinated derivate of cinnarizine. It has antihistaminic and CNS depressant effects, but is mainly used as an inhibitor of central and peripheral vasoconstriction.

Buflomedil hydrochloride produces a number of pharmacological effects including nonspecific inhibition of  $\alpha$ -adrenoceptors in vascular smooth muscle, inhibition of platelet aggregation, improved erythrocyte deformability, nonspecific calcium antagonistic activity and oxygen-sparing activity. It is used in the treatment of peripheral occlusive arterial diseases.

Considerations on splitting the ATC-group C07AA  
(Beta blocking agents, plain, non-selective).

This group is represented by:

C07AA01; Alprenolol  
C07AA02; Oxprenolol  
C07AA03; Pindolol  
C07AA05; Propranolol  
C07AA06; Timolol  
C07AA16; Tertatolol  
C07AA23; Penbutolol  
C07AA07; Sotalol

The ATC-group has been split into two groups

0C07AAB0 V with  
C07AA01; Alprenolol  
C07AA02; Oxprenolol  
C07AA03; Pindolol  
C07AA05; Propranolol  
C07AA06; Timolol  
C07AA16; Tertatolol  
C07AA23; Penbutolol

0C07AAC0 QV with  
C07AA07; Sotalol

The rationale for the division of the C07AA ATC-group lies in the additional mode of action that sotalol displays. Apart from being a noncardioselective  $\beta$ -blocking agent like the other  $\beta$ -blockers in this ATC-group, it has class III antiarrhythmic activity, according to the classification of Vaughan-Williams.

Considerations on splitting the ATC-group G01AF (imidazole derivatives).

This group is represented by:

G01AF03; Tinidazole  
G01AF01; Metronidazole  
G01AF02; Clotrimazole  
G01AF04; Miconazole  
G01AF05; Econazole  
G01AF07; Isoconazole  
G01AF09; Terconazole

The ATC-group has been split into three groups

OG01AFB0 QV (oral preparations) with  
G01AF03; Tinidazole

OG01AFBV V (vaginal preparations) with  
G01AF01; Metronidazole

OG01AFCV V (vaginal preparations) with  
G01AF02; Clotrimazole  
G01AF04; Miconazole  
G01AF05; Econazole  
G01AF07; Isoconazole  
G01AF09; Terconazole

The rationale for the division of the G01AF ATC-group is based on the differences in chemical structure, modes of action and indications between the OG01AFBV V and OG01AFB0 V group versus the OG01AFCV V group.

Tinidazole and metronidazole are 5-nitroimidazole derivatives. Their mode of action is thought to involve interference with DNA. They are used in the treatment of giardiasis and of vulvovaginitis caused by trichomonas.

The OG01AFCV V group contains only imidazole derivatives. Their mode of action is similar to ketoconazole. These substances interfere with the ergosterol synthesis. They alter the permeability of the cell membrane of sensitive fungi. Their indications are the treatment of vaginal infections caused by candida species. Except for terconazole they are used in the treatment of pityriasis versicolor and erythrasma too.

Considerations on splitting the ATC-group G03DA (pregnen derivatives).

This group is represented by:  
G03DA02; Medroxyprogesterone  
G03DA04; Progesterone  
G03DA05; Gestrinon

The ATC-group has been split into the separate substances.

OG03DAB0 with  
G03DA02; Medroxyprogesterone

OG03DAD0 QV with  
G03DA04; Progesterone

OG03DAE0 QV with  
G03DA05; Gestrinone

The rationale for the division of the G03DA ATC-group is based on the differences in indications of the various substances. Progesterone is used in the treatment of menstrual disorders and irregularities, in combination with oestrogens for anticonception and in the treatment of endometriosis and premenstrual syndrome. It is sometimes added to the treatment of osteoporosis to reduce the increased risk of endometrial hyperplasia and carcinoma when patients are treated with oestrogens for a longterm period.

Medroxyprogesterone, a synthetic progestagen, has similar actions to the progestagens in general. Apart for being used for menstrual disorders and irregularities and endometriosis, it has a specific application in the therapy of some hormone dependant malignant neoplasms, such as breast, endometrial, renal and prostatic carcinoma. (in higher doses; see L02AB ATC-group).

Gestrinone has androgenic, antiprogestagenic and antioestrogenic properties. It is mainly used in the treatment of endometriosis.

Considerations on splitting the ATC-group G03DC (estren derivatives).

This group is represented by:

G03DC01; Allylestrenol  
G03DC02; Norethisterone  
G03DC03; Lynestrenol  
G03DC05; Tibolone

The ATC-group has been split into three groups

OG03DCB0 QV with  
G03DC01; Allylestrenol

OG03DCC0 V with  
G03DC02; Norethisterone  
G03DC03; Lynestrenol

OG03DCD0 QV with  
G03DC05; Tibolone

The rationale for the division of the G03DC ATC-group is based on the differences in indications of the various substances. Norethisterone and lynestrenol are used in oral anticonception.

Allylestrenol is used in habitual and threatened abortion. It has no androgenic properties, therefore lessening the risk of possible virilisation effects on the foetus.

Tibolone is reported to have androgenic, oestrogenic and progestagenic properties and is used in the treatment of menopausal and postmenopausal symptoms.

Considerations on splitting the ATC-group G04AB (pyridone derivatives).

This group is represented by:

G04AB01; Nalidixic acid

G04AB03; Pipemidic acid

The ATC-group has been split into the separate substances.

0G04AB00 QK (oral preparations for children) with

G04AB01; Nalidixic acid

0G04AB00 V

G04AB01; Nalidixic acid

1G04AB00 V with

G04AB03; Pipemidic acid

Nalidixic acid and pipemidic acid are both quinolones. The first substance is a first generation quinolone and the latter substance a second generation quinolone. The basis for the division of the G04AB ATC-group is that the later generations quinolones are effective in a much lower dose than nalidixic acid. As a result of the lower therapeutic dose, fewer adverse effects are seen with the second quinolone generation and furthermore, an additional bactericidal spectrum is seen in the later developed agents of the second generation.

Considerations on splitting the ATC-group G04AG (other urinary antiseptics and antiinfectives).

This group is represented by:

G04AG03; Cinoxacin  
G04AG06; Nitroxoline  
G04AG04; Norfloxacin

The ATC-group has been split into two groups

1G04AGB0 V with  
G04AG03; Cinoxacin  
G04AG06; Nitroxoline

2G04AGC0 V with  
G04AG04; Norfloxacin

The basis for the division of the G04AG ATC-group is the improved efficacy of later quinolone generations as expressed in the lower minimal inhibiting concentration and the wider bactericidal spectrum of the later generation. Cinoxacin and the nalidixic acid related nitroxoline belong to the older quinolone related substances. Norfloxacin being of the third generation of quinolones has, apart from the inhibitive action on DNA gyrase similar to cinoxacin and nitroxoline, an inhibitive action on RNA and protein synthesis. Norfloxacin can be used against gram negative bacteria and pseudomonas as well as against some gram positive species such as staphylococcus.

Considerations on splitting the ATC-group H02AB (glucocorticoids).

This group is represented by:

H02AB01; Betamethasone  
H02AB02; Dexamethasone  
H02AB03; Fluocortolone  
H02AB04; Methylprednisolone  
H02AB05; Paramethasone  
H02AB06; Prednisolone  
H02AB07; Prednisone  
H02AB08; Triamcinolone  
H02AB09; Hydrocortisone  
H02AB10; Cortisone

The ATC-group has been split into two groups

OH02ABB0 V with

H02AB01; Betamethasone  
H02AB02; Dexamethasone  
H02AB03; Fluocortolone  
H02AB04; Methylprednisolone  
H02AB05; Paramethasone  
H02AB06; Prednisolone  
H02AB07; Prednisone  
H02AB08; Triamcinolone

OH02ABC0 V with

H02AB09; Hydrocortisone  
H02AB10; Cortisone

The rationale for the division of the H02AB ATC-group is based on the differences in indications of hydrocortisone and cortisone compared with the other substances in the ATC-group. Cortisone and its metabolite hydrocortisone have a considerable stronger mineralcorticoid effect than the other corticosteroids in the ATC-group. For this reason hydrocortisone and cortisone are mainly used in substitution therapy. For anti-inflammatory and immunosuppressive indications the other substances are more suitable.

Considerations on splitting the ATC-group J01AA (tetracyclines).

This group is represented by:

J01AA01; Demeclocyclin

J01AA02; Doxycyclin

J01AA07; Tetracyclin

J01AA08; Minocyclin

The ATC-group has been split into the following groups.

OJ01AAB0 QV with  
J01AA01; Demeclocyclin

OJ01AAC0 K (oral preparations for children) with  
J01AA02; Doxycyclin

OJ01AAC0 V with  
J01AA02; Doxycyclin

OJ01AAD0 V with  
J01AA07; Tetracyclin  
J01AA08; Minocyclin

The rationale for the division of the J01AA ATC-group is based on the differences in indications and adverse effects of the substances in this ATC-group.

Demeclocyclin has more serious adverse effects than doxycyclin, minocyclin and tetracyclin.

Doxycyclin is used as a broad spectrum antibiotic because of its pharmacological properties. Tetracyclin and minocyclin are broad spectrum antibiotics too but doxycyclin is preferred as such. Tetracyclin and minocyclin are recommended in the treatment of acne vulgaris.

Considerations on splitting the ATC-group M01AA (Butylpyrazolidines).

This group is represented by:

M01AA01; Phenylbutazone  
M01AA03; Oxyphenbutazone  
M01AA04; Azapropazone

The ATC-group has been split into three groups

0M01AAB0 QV with  
M01AA01; Phenylbutazone

0M01AAC0 V with  
M01AA01; Phenylbutazone  
M01AA03; Oxyphenbutazone

1M01AAC0 V with  
M01AA04; Azapropazone

The rationale for the division of the M01AA ATC-group is based on the differences in adverse effects of phenylbutazone and oxyphenbutazone versus azapropazone. Azapropazone has much less serious adverse effects than the other substances in this ATC-group.

Considerations on splitting the ATC-group M01CA (quinolines):

This group is represented by:

M01CA01; Chloroquine

M01CA02; Hydroxychloroquine

The ATC-group has been split into the separate substances.

OM01CAB0 V with

M01CA01; Chloroquine

OM01CAC0 QV with

M01CA02; Hydroxychloroquine

The rationale for the division of the M01CA ATC-group is based on the differences in adverse effects of the two substances. Chloroquine seems to have more serious adverse effects on the eye than hydroxychloroquine in the chronic treatment of lupus erythematosus and rheumatoid arthritis. Therefore the two substances have been put into different groups.

Considerations on splitting the ATC-group N04AA  
(tertiary amines with a carbon chain)

This group is represented by:

N04AA01; Trihexyphenidyl  
N04AA02; Biperidene  
N04AA03; Metixene  
N04AA04; Procyclidine  
N04AA08; Dexetimide  
N04AA06; Tolperison

The ATC-group has been split into two groups

1N04AAB0 V with  
N04AA01; Trihexyphenidyl  
N04AA02; Biperidene  
N04AA03; Metixene  
N04AA04; Procyclidine  
N04AA08; Dexetimide

0N04AAC0 QV with  
N04AA06; Tolperisone

The rationale for the division of the N04AA ATC-group is based on differences in modes of action and differences in indications.

Trihexyphenidyl, biperidene, metixene, procyclidine and dexetimide are parasympatholytic agents used in Parkinsons disease.

Tolperisone is a centrally acting muscle relaxant used in the treatment of muscle spasms.

Considerations on splitting the ATC-group N05AL (benzamides).

This group is represented by:

N05AL01; Sulpiride

N05AL02; Tiapride

The ATC-group has been split into two groups

ON05AXC0 QV with  
N05AL01; Sulpiride

ON05AXD0 QV with  
N05AL02; Tiapride

The rationale for the division of the N05AL ATC-group is based on the differences in indications between sulpiride and tiapride.

Sulpiride is claimed to exert its antipsychotic action via a selective blockade of the central dopamine D2-receptors. It has been used in the treatment of psychotic disorders and vertigo.

Tiapride is used in the treatment of tardive dyskinesia. It is not used as an antipsychotic as opposed to sulpiride although it has general properties similar to sulpiride.

Considerations on splitting the ATC-group N07AA  
(anticholinesterases)

This group is represented by:

N07AA01; Neostigmine  
N07AA02; Pyridostigmine  
N07AA03; Distigmine

The ATC-group has been split into the separate substances.

ON07AAB0 V with  
N07AA01; Neostigmine

ON07AAC0 QV with  
N07AA02; Pyridostigmine

ON07AAD0 QV with  
N07AA03; Distigmine

The rationale for the division of the N07AA ATC-group is based on differences in indications and adverse effects of the various substances in this ATC-group. Neostigmine, has more muscarine adverse effects than pyridostigmine. Pyridostigmine, having less adverse effects than neostigmine, has the advantage of acting longer than neostigmine. Distigmine too exerts an action similar to neostigmine but more prolonged. It is used in the treatment of myasthenia gravis where it is combined with short-acting parasympathomimetics.

Considerations on splitting the ATC-group R03AC  
(selective  $\beta_2$ -adrenoceptor agonists).

This group is represented by:

R03AC02; Salbutamol  
R03AC03; Terbutaline  
R03AC04; Fenoterol  
R03AC05; Rimiterol

The ATC-group has been split into two groups

**O**R03ACBII V with  
R03AC02; Salbutamol  
R03AC03; Terbutaline  
R03AC04; Fenoterol

**O**R03ACCIDQV with  
R03AC05; Rimiterol

The rationale for the division of the R03AC ATC-group is based on the pharmacokinetic properties and the concomitant indications of the two groups.

Rimiterol has a very short half-life and is therefore only used in the treatment of acute exacerbations of asthma bronchiale. The other agents are used in the prevention of asthma bronchiale.

Considerations on splitting the ATC-group R03DA (xanthines).

This group is represented by:  
R03DA02; Cholinetheophyllinate  
R03DA04; Theophylline  
R03DA05; Aminophylline

The ATC-group has been split into six groups, three in each age group.

OR03DAB0 QK (oral preparations for children) with  
R03DA04; Theophylline

OR03DABR K (rectal preparations for children) with  
R03DA04; Theophylline  
R03DA05; Aminophylline

OR03DAC0 K (oral preparations for children) with  
R03DA04; Theophylline

OR03DAB0 V (oral preparations for adults) with  
R03DA02; Cholinetheophyllinate  
R03DA05; Aminophylline

OR03DABR V (rectal preparations for adults) with  
R03DA04; Theophylline  
R03DA05; Aminophylline

OR03DAC0 V (oral preparations for adults) with  
R03DA04; Theophylline

The rationale for the division of the R03DA ATC-group is based on differences between the adverse effects of the sustained release oral preparations in comparison to the "normal" oral tablets. The amount of adverse effects is related to the plasmaconcentration of the substance. The use of slow release preparations ensures minimal fluctuations of the plasma concentration thus minimizing the occurrence of adverse effects. The OR03DAC0 K and the OR03DAC0 V groups contain the slow release preparations of theophylline.

Considerations on splitting the ATC-group R06AD  
(Phenothiazine derivatives)

This group is represented by:

R06AD01; Alimemazine  
R06AD02; Promethazine  
R06AD03; Thiethylperazine  
R06AD08; Oxomemazine

The ATC-group has been split into the separate substances.

OR06AD10 QV with  
R06AD01; Alimemazine

OR06AD20 QK (oral preparations for children) with  
R06AD01; Alimemazine

OR06AD20 QV with  
R06AD01; Alimemazine

OR06ADC0 K (oral preparations for children) with  
R06AD02; Promethazine

OR06ADC0 V with  
R06AD02; Promethazine

OR06ADD0 QV with  
R06AD03; Thiethylperazine

OR06ADDR QV with  
R06AD03; Thiethylperazine

OR06ADG0 QK (oral preparations for children) with  
R06AD08; Oxomemazine

OR06ADG0 QV with  
R06AD08; Oxomemazine

The rationale for the division of the R06AD ATC-group is based on the differences in indications and adverse effects of the separate substances.

Alimemazine has antihistaminic and antipsychotic properties. Because of its antipsychotic actions, alimemazine displays adverse effects which other substances in this ATC-group display to a much lesser extent.

Promethazine, in the first place, is used as a sedative.

Thiethylperazine has similar properties to those of chlorpromazine. It is mainly used in the treatment of nausea and vomiting.

Oxomemazine is used in the treatment of coughing.

Considerations on splitting the ATC-group R06AX (other antihistamines for systemic use).

This group is represented by:

R06AX02; Cyproheptadine  
R06AX11; Astemizole  
R06AX12; Terfenadine  
R06AX13; Loratadine  
R06AX17; Ketotifen

The ATC-group has been split into six groups, three in each age group.

OR06AXB0 QK (oral preparations for children) with  
R06AX02; Cyproheptadine

OR06AXB0 QV with  
R06AX02; Cyproheptadine

OR06AXC0 K (oral preparations for children) with  
R06AX11; Astemizole  
R06AX12; Terfenadine

OR06AXC0 V with  
R06AX11; Astemizole  
R06AX12; Terfenadine  
R06AX13; Loratadine

OR06AXD0 QK (oral preparations for children) with  
R06AX17; Ketotifen

OR06AXD0 QV with  
R06AX17; Ketotifen

The rationale for the division of the R06AX ATC-group is based on differences in modes of action and of the adverse effects. Astemizole, terfenadine and loratadine are H<sub>1</sub>-antihistaminic agents which do not cause sedation.

Cyproheptadine has a wider range of actions than the other sedative antihistamines. Apart from having antihistaminic and serotonin-antagonist activity, it has antimuscarinic activity and calcium blocking properties. It is used in the treatment of anorexia nervosa besides its use as an antihistaminic agent.

Ketotifen has besides H<sub>1</sub>-antihistaminic properties, mast cell stabilising properties analogous to those of sodium cromoglycate. Therefore it is used in the prophylaxis of asthma.

Examples of differences between the MRC and the ATC classification

Discussion:

ATC-group A02BX

The practice of the WHO CC has been to leave new drug substances in the X-group until more is known about the actual use of the drug.

In the MRS, these X-groups will be divided into different groups which will receive separate codes.

It was decided that the WHO CC as far as possible would try to establish special groups for drugs at the 4th level, thereby avoiding too many different drugs in the X-group.

ATC-group A07DA and A07EC

Since it is difficult for the WHO CC to take differences in mode of action and adverse drug reaction pattern into consideration in their ATC-classification, it was decided that this type of differentiation could be better dealt with by using an additional code.

ATC-group C01DA- anti-anginal vasodilators

The participants from The Netherlands felt that oxyfedrine should not be classified together with nitroglycerine.

It was decided that this classification should be reconsidered by the WHO CC.

ATC-group C02DE- calciumantagonists

The WHO CC informed the meeting that the subclassification within this group had been discussed.

It was decided that the classification should be reconsidered by the WHO CC.

ATC-group C04AX- peripheral vasodilators

The WHO CC argued that this was a problematic group and that they would prefer to keep the classifications as they stood for the time being.

ATC-group C07AA - betablockers

The Dutch participants argued that sotalol had arrhythmias as its main indication and that it should, therefore, should be separated from the other betablockers.

ATC-group G01AF - imidazole-derivatives

The WHO CC informed the meeting that, at present, they were discussing a regrouping within the anti-infectives group, moving metronidazole to group P.

ATC-group G03DA

No changes in the ATC-classification.

ATC-group G03DC

The main problem when classifying drugs belonging to this group is that the difference between the groups is mainly chemical and it is difficult to explain chemical differences when naming the groups.

This group will be reconsidered by the WHO CC.

ATC-group G04AB

The classification of chemotherapeutics used in UTI is difficult and is at present being reconsidered by the WHO CC together with the classification of quinolones.

ATC-group H02AB

It was decided that The Netherlands would propose a new classification of this particular group and give their reasons for why the present ATC-classification should be changed.

The proposal will then be considered by the WHO CC in the usual way.

ATC-group J01AA

The WHO CC informed that it would not be possible to sub-classify those tetracyclines that were used in acne.

ATC-group M01AA - butylpyrazolidines

In the ATC-classification difunizal is classified in group N; in The Netherlands the substance is classified in group M.

It was felt that the borderline between substances used for pain (group N9) and the substances used in muscle-skeletal disorders (group M) was not clear in all cases.

It was decided that cross-references should be used in these cases.

ATC-group M01CA

The WHO CC informed that chloroquine and hydroxichloroquine had been moved to group P.

ATC-group N04 AA

The WHO CC will consider moving tolperisone (a muscle relaxant) to group M03EX

ATC-group N05AL

The WHO CC will reconsider the classification of tiapride.

ATC-group N07AA - anticholinesterases

The ATC-classification will not be changed. Further adaptations could be introduced in the additional MRC coding.

ATC-group R03AC - beta-2-agonists

The WHO CC informed that it would be difficult to divide the group according to the severity of the indication (different degrees of the severity of asthma). Such differences could better be reflected in the additional MRC-coding.

ATC-group R03DA

The WHO CC informed that it would be difficult to divide the retarded formulations for theophylline and do the same for other substances.

ATC-group R06AD

The antihistamines are classified according to their therapeutic use.

ATC-group R06AX

When classifying antihistamines it is difficult to take the sedative effect into consideration since this effect to a large extent will be dose-related in most cases.

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