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Reassessment of reimbursement status for medicinal products in ATC groups C02, C03, C07, C08 and C09

Background and content

As part of the reassessment process, the Danish Medicines Agency has requested that the Reimbursement Committee reassess the reimbursement status for medicinal products in ATC groups C02 (antihypertensives), C03 (diuretics), C07 (beta blocking agents), C08 (calcium channel blockers) and C09 (ACE inhibitors, angiotensin II antagonists and renin inhibitors). Appendices **A1-A5** are graphic overviews of the substances in each individual group.

The medicinal products in ATC groups C02, C03, C07, C08 and C09 are all used to varying degrees for the treatment of hypertension and a number of cardiovascular diseases. The Committee has assessed the reimbursement status for these medicinal products, and this recommendation is an overall recommendation for all[1] medicinal products in ATC groups mentioned above, which have been authorised for marketing in Denmark, and for which a price has been notified to the Danish Medicines Agency as of 13 January 2008.

Below is the Reimbursement Committee's recommendation for the future reimbursement status for the medicinal products followed by a review of the reassessment process, the overall viewpoints and reasons of the Committee in relation to the medicinal products and the recommendation and finally more specific comments on each individual active substance group and any combination medicinal products.

The enclosed Appendices **B1-B5** provide a more detailed overview of the active substances in the five different ATC subgroups specifying the approved indication for the medicinal product containing the substance in question which has been authorised for the longest period of time, pharmaceutical form, names of medicinal products, dispensing terms, current reimbursement status, price of treatment per

[1] The Reimbursement Committee's reassessment and this recommendation do not, however, comprise medicinal products with limited dispensing status ("BEGR" and "AP4BG"), herbal medicinal products, strong vitamin or mineral products and radiopharmaceuticals.

day, consumption and the Committee's specific comments on and recommendation for reimbursement status for each individual active substance and pharmaceutical form in the group.

There are relatively many medicinal products with combinations of two substances within these groups. They are processed under the group to which their ATC code belongs.

The Reimbursement Committee's recommendation

The Reimbursement Committee recommends to the Danish Medicines Agency that:

1.
All medicinal products in ATC group C02 (antihypertensives)[2] containing

the individual substances: methyldopa or moxonidine

maintain their current reimbursement status.
The Reimbursement Committee recommends to the Danish Medicines Agency that no case be opened on changing the reimbursement status for these medicinal products.

2.
All medicinal products in ATC group C03 (diuretics) containing

the individual substances:	bendroflumethiazide, indapamide, furosemide, bumetanide, spironolactone or eplerenon
the combinations:	bendroflumethiazide and potassium, bumetanide and potassium, hydrochlorothiazide and amiloride, furosemide and amiloride.

maintain their current reimbursement status.
The Reimbursement Committee recommends to the Danish Medicines Agency that no case be opened on changing the reimbursement status for these medicinal products.

3.
Oral medicinal products in ATC group C07 (beta blocking agents) containing

the individual substances:	pindolol, propranolol, sotalol, metoprolol, atenolol, acebutolol, bisoprolol, nebivolol, labetalol or carvedilol
the combinations:	metoprolol and hydrochlorothiazide, atenolol and chlorothalidone, metoprolol and felodipine

maintain their current reimbursement status.
The Reimbursement Committee recommends to the Danish Medicines Agency that no case be opened on changing the reimbursement status for these medicinal products.

[2] Doxazosin (C02CA04) is reassessed together with medicinal products used for the treatment of prostatic hyperplasia, cf. the section on the viewpoints of the Reimbursement Committee in relation to medicinal products in ATC group C02 (antihypertensives).

4.
Medicinal products for injection in ATC group C07 (beta blocking agents) containing

the individual substances: sotalol, metoprolol and labetalol

have their reimbursement status changed.
The Reimbursement Committee recommends to the Danish Medicines Agency that a case be opened on changing the reimbursement status for these medicinal products, so that they no longer be granted general or general limited reimbursement.

5.
All medicinal products in ATC group C08 (calcium channel blockers) containing

the individual substances:	amlodipine, felodipine, isradipine, nifedipine, nitrendipine, lacidipine, lercanidipine, verapamil or diltiazem
the combination:	verapamil and trandolapril

maintain their current reimbursement status, cf., however, item 6.
The Reimbursement Committee recommends to the Danish Medicines Agency that no case be opened on changing the reimbursement status for these medicinal products.

6.
The Reimbursement Committee recommends to the Danish Medicines Agency that a case be opened on changing the reimbursement for nimodipine (C08CA06) with a view to granting general reimbursement.

7.
All medicinal products in ATC groups C09A and C09B (ACE inhibitors) containing

the individual substances:	captopril, enalapril, lisinopril or ramipril
the combinations:	captopril and hydrochlorothiazide, enalapril and hydrochlorothiazide, lisinopril and hydrochlorothiazide, ramipril and hydrochlorothiazide

maintain their current reimbursement status.
The Reimbursement Committee recommends to the Danish Medicines Agency that no case be opened on changing the reimbursement status for these medicinal products.

8.
All medicinal products in ATC groups C09A and C09B (ACE inhibitors) containing

the individual substances:	perindopril, quinapril, benazepril, fosinopril or trandolapril
the combination:	perindopril and indapamide

have their reimbursement status changed.

The Reimbursement Committee recommends to the Danish Medicines Agency that a case be opened on changing the reimbursement status for these medicinal products, so that they no longer be granted general or general limited reimbursement.

9.
All medicinal products in ATC groups C09C and C09D (angiotensin II antagonists) and C09X (renin inhibitors) containing

the individual substances:	losartan, eprosartan, valsartan, irbesartan, candesartan, telmisartan, olmesartan or aliskiren
the combinations:	losartan and hydrochlorothiazide, eprosartan and hydrochlorothiazide, valsartan and hydrochlorothiazide, irbesartan and hydrochlorothiazide, candesartan and hydrochlorothiazide, telmisartan and hydrochlorothiazide, olmesartan and hydrochlorothiazide, valsartan and amlodipine

have their reimbursement status changed and be granted general limited reimbursement with the following limitation:

> "Patients with hypertension or any other type of cardiovascular disease requiring treatment, where treatment with cheaper medicinal products eligible for general reimbursement with an effect on the rennin-angiotensin system has shown to be inadequate, or patients who cannot tolerate these medicinal products."

The Reimbursement Committee recommends to the Danish Medicines Agency that a case be opened on changing the reimbursement status for these medicinal products.

Reassessment process

In a letter dated 13 June 2005, the Danish Medicines Agency informed all companies holding a marketing authorisation for human medicinal products[3] that the process of reassessing the reimbursement status for, among others, medicinal products in ATC group C (cardiovascular system) would be initiated. A number of scientific societies and patient groups received the same information in a letter dated 20 June 2005. In letters dated 1 November 2006, 18 November 2006 and 21 November 2006, the same stakeholders were informed that the reassessment would comprise the medicinal products in groups C03 (diuretics), C08 (calcium channel blockers) and C09 (ACE inhibitors and angiotensin II antagonists).

The first time the Reimbursement Committee discussed the reimbursement status for medicinal products in ATC groups C03, C08 and C09 was at a meeting held on 17 January 2006.

Following a request by letter dated 6 March 2006 from the Reimbursement Committee, the Danish Medicines Agency asked a number of scientific societies for their views on a number of questions about hypertension treatment in Denmark, and at the same time medicinal products in ATC group C07 (beta blocking agents) were included in the reassessment. The societies in question, which all replied to the request, were the Danish Hypertension Society, the Danish Society of Internal Medicine, the Danish

[3] With the exception of companies holding a marketing authorisation for medicinal products with limited dispensing status, herbal medicinal products, strong vitamin and mineral products and radiopharmaceuticals.

College of General Practitioners, the Danish Society of Nephrology, the Danish Society of Cardiology, the Danish Endocrine Society and the Danish Medical Society.

In addition, the Danish Stroke Association, the Danish Heart Foundation and the Danish Diabetes Association provided their views.

In an announcement published on 4 July 2006 on the Danish Medicines Agency's website, medicinal products in ATC group C02 (antihypertensives) were also included, so that reimbursement for all medicinal products which can be used for hypertension treatment is reassessed at the same time.

All replies and contributions and replies have been published on the Danish Medicines Agency's website[4] and have been presented to the Reimbursement Committee. The viewpoints stated have all been taken into consideration by the Committee.

The Reimbursement Committee has subsequently discussed the reimbursement status for these medicinal products at meetings held on 12 December 2006, 20 February 2007, 25 September 2007 and 22 January 2008.

The Reimbursement Committee's overall comments and reasons

Introduction

The Reimbursement Committee has based its discussions on the Danish Medicines Agency's guideline of 8 June 2005 on the procedure for reassessment of the reimbursement status for medicinal products and the Danish Medicines Agency's guidelines of 4 July 2006 for assessment and comparison of medicinal products in connection with the reassessment of the reimbursement status for medicinal products.

A common characteristic of the medicinal products in ATC groups C02, C03, C07, C08 and C09 is that the majority of them, to varying degrees, are used for the treatment of hypertension. The Committee has, however, emphasised that many of the medicinal products are used for the treatment of other diseases, primarily cardiovascular diseases, e.g. heart insufficiency, angina pectoris, arrhythmia, generalised oedema and microalbuminuria, and that many of the medicinal products have different adverse reaction profiles and interaction patterns. It is thus a complex group of medicinal products.

The Committee's assessment of the use of the different active substances is based on the Committee's clinical experience and the recommendations stated in clinical guidelines etc., cf. the list of references, rather than the medicinal products' approved indications, which may differ considerably, irrespective of whether the medicinal products are used in the same way in everyday clinical use.

The Committee's assessment of the price of treatment per day for each individual active substance has been made in accordance with the above guidelines for the assessment and comparison of medicinal products in connection with the reassessment of reimbursement status. The calculations are based on the equieffective doses recommended by the Institute for Rational Pharmacotherapy (IRF) in the National

[4] www.dkma.dk > Companies > General reimbursement > Reassessment of reimbursement status for medicinal products: http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=10459

Recommendation List for ATC groups C03, C07, C08 and C09 as of 7 February 2005[5] (alternatively DDD or other values) as well as reimbursement prices[6] for each individual substance.

The Committee's recommendation is based on the reimbursement prices of the medicinal products for the past three months (six price periods, the first period starting on 22 October 2007 and the last period starting on 31 December 2007). As the Committee has discussed the reimbursement status for the medicinal products at a number of meetings, cf. above, the Committee has been following the development in the price of the medicinal products for a long period of time, and the Committee points out that the reassessment of the reimbursement status for the medicinal products should be seen in the light of the fact that in Denmark there is free pricing of medicinal products and that companies can report price changes every two weeks.

Appendices C1-C5 are price lists for all medicinal products based on the reimbursement prices of the medicinal products for six price periods with specification of the doses and strengths used. **Appendix D** explains the lists.

The discussions and the recommendation of the Reimbursement Committee are also based on information on the consumption and the development in the consumption in ATC groups C02, C03, C07, C08 and C09. Data on the consumption and sales of each individual active substance and substance group as well as the number of persons being treated with these medicinal products are available at the Danish Medicines Agency's website, www.medstat.dk[7].

In its recommendation, the Committee has proposed changes in the future reimbursement status for the medicinal products in those instances where the Committee considers the consumption of the medicinal products not to be rational and where changes in the reimbursement status are expected to support a rational use of the medicinal products. The Committee also recommends that it should be easy for doctors to prescribe medicinal products rationally.

The Reimbursement Committee's recommendation and related reasons are to a large extent based on active substance types, but it should be noted that the Committee's assessment comprises a decision on the individual medicinal products and their use.

Combinations and good use of medicinal products
Patients being treated with medicinal products comprised by this reassessment often have several diseases requiring treatment, including heart disease, apoplexy, diabetes or hypertension. Four to five different medicinal products may be used in the treatment of hypertension alone.

The patients' consumption of medicinal products generally includes several or many different medicinal products, both medicinal products comprised by this reassessment and other medicinal products. In accordance with the replies from several of the scientific societies, the Committee has thus in its assessment of combination products which are comprised by the reassessment emphasised the need for combination treatment and for supporting good use of medicinal products/compliance.

[5] http://www.irf.dk/dk/rekommandationsliste/national_rekommandationsliste.htm (in Danish only)
[6] For medicinal products eligible for reimbursement, the reimbursement prices of the medicinal products are used; for medicinal products not eligible for reimbursement, the lowest prices are used.
[7] http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=1673

Hypertension
As most of the substance types in question to a large extent are intended for the treatment of hypertension, the Reimbursement Committee has in particular focused on the treatment of hypertension, but the Committee has also emphasised that many of the active substances are also used for the treatment of other diseases.

The Reimbursement Committee shares the general opinion of clinicians that hypertension is undertreated in Denmark, and that it is important to support the widespread treatment of hypertension. Too few persons are being treated, and of those being treated not everyone meets the treatment targets. Several observations support this view, e.g. the Copenhagen City Heart Study (*Østerbroundersøgelsen*)[8].

As a starting point, the Reimbursement Committee is of the opinion that the distribution between monotherapy and the different treatments using multiple substances should be approx. 20 per cent with one substance, approx. 30 per cent with two substances, approx. 30 per cent with three substances and approx. 20 per cent with four substances or more. This is supported by the replies from the Danish Hypertension Society and the Danish Society of Cardiology. Figures from the Danish Medicines Agency's Register of Medicinal Product Statistics showed that in 2006 the actual distribution was approx. 43 per cent with one substance, 37 per cent with two substances, 17 per cent with three substances and 4 per cent with four substances. For this reason, among others, the Committee is therefore of the opinion that there is still a need for a more intensive treatment, even though the biggest challenge probably is to trace the undiagnosed hypertension patients.

The different types of antihypertensives, diuretics (thiazides), beta blocking agents, calcium channel blockers, ACE inhibitors and angiotensin II antagonists are generally considered to be equally effective in terms of lowering the blood pressure and preventing blood pressure-related diseases in patients with hypertension without other diseases, cf., however, the section on beta blocking agents. None of the substance groups mentioned can generally be said to be absolute first-line treatment of hypertension, but they are all potential first-line treatment, with the proviso as to beta blocking agents mentioned above.

In its discussions on class effect within the different treatment modalities of hypertension, the Reimbursement Committee has emphasised that the scientific societies in their replies have not questioned class effects. The same applies to NICE and the Task Force for Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) in their respective clinical guidelines[9] [10].

For patients with other diseases requiring treatment, the choice of substance types and the sequence in which they are introduced in the treatment depend on the patient's other diagnoses and the degree of hypertension.

Even though several of the medicinal product groups are used as first-line treatment of hypertension, the Committee has not compared the medicinal products in terms of price across the overall ATC groups. As mentioned above, this is because the Committee has emphasised the different uses, interaction patterns and adverse reaction profiles of the medicinal products, both within the different groups and between the groups. Despite occasionally relatively large price gaps within a group, the Committee has therefore not necessarily found reasons for proposing changes in the reimbursement status.

[8] The Copenhagen City Heart Study (*Østerbroundersøgelsen*)
[9] www.nice.org: http://www.nice.org.uk/guidance/index.jsp?action=byID&o=10986
[10] www.jhypertension.com

Medicinal products in ATC group C09 (ACE inhibitors, angiotensin II antagonists and renin inhibitors) differ from the medicinal products in groups C02, C03, C07 and C08 as this group is characterised by a more limited application area and a higher degree of uniformity in terms of class effect than the others. The medicinal products in group C09 are thus recommended equally. At the same time, the Committee recognises that some patients, who cannot be identified beforehand, experience adverse reactions, e.g. cough, when using ACE inhibitors, and that these patients instead often can be treated with angiotensin II antagonists.

Some ACE inhibitors, captopril, enalapril, lisinopril and ramipril, are cheaper than the other ACE inhibitors and all angiotensin II antagonists and should thus, in the opinion of the Committee, be first-line treatment. In the opinion of the Committee, a considerable part of the consumption in ATC group C09 is not rational as for 46 per cent of the patients for which treatment with an angiotensin II antagonist was initiated in 2006 no prior attempt had been made to use an ACE inhibitor[11]. This share remains unchanged in the first three quarters of 2007. In addition to this, figures from the Danish Medicines Agency's Register of Medicinal Product Statistics show that for the first ten months of 2007 20 per cent of the patients being treated with an ACE inhibitor are being treated with one of the five most expensive ACE inhibitors, corresponding to 49 per cent of the total expenses for treatment with ACE inhibitors. This is described in more detail in the section on medicinal products in ATC group C09.

To support rational use of medicinal products, the Committee thus recommends that the reimbursement for the most expensive ACE inhibitors, perindopril, quinapril, benazepril, fosinopril and trandolapril, as well as the combination with perindopril and indapamid be removed, and that the reimbursement for all angiotensin II antagonists in ATC groups C09C, C09D and C09X be limited to patients with hypertension or any other type of cardiovascular disease requiring treatment, where treatment with cheaper medicinal products eligible for general reimbursement with an effect on the renin-angiotensin system has shown to be inadequate, or patients who cannot tolerate these medicinal products. The reasons for the recommendations are stated in the section on the Committee's viewpoints and reasons in relation to medicinal products in ATC group C09 (ACE inhibitors, angiotensin II antagonists and renin inhibitors).

The Reimbursement Committee is of the opinion that by encouraging doctors, as a starting point, to use the cheaper medicinal products eligible for general reimbursement (unlimited) in the treatment you support the rational use of medicinal products, and the Reimbursement Committee also finds this to be in line with the obligation of doctors – in accordance with the Danish Act on General Practitioners (*Lægeloven*) – to prescribe treatment that is cost-effective for both patients and society. At the same time, the Committee emphasises that the treatment of patients is not deteriorated.

In addition to the proposed changes for medicinal products in ATC group C09, the recommendation also includes a proposed change in reimbursement status for nimodipine (C08CA06) with a view to granting general reimbursement, cf. the section on the Committee's viewpoints in relation to medicinal products in ATC group C08 (calcium channel blockers). The Committee also recommends that injection fluids with the active substances sotalol, metoprolol and labetalol in ATC group C07 in future should not be granted general reimbursement as the medicinal products in the opinion of the Committee should only be used in hospitals, cf. the section on the Committee's viewpoints in relation to medicinal products in ATC group C07 (beta blocking agents).

[11] http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=6434

Final general comments
Undertreatment of hypertension is a focus area for many, including the scientific societies, the Danish Stroke Association, the Danish Heart Foundation, the Danish Diabetes Association and the Institute for Rational Pharmacotherapy. As mentioned above, the Committee shares this opinion, and this has been an important element in the considerations of the Reimbursement Committee.

As the Committee also wants to see a more widespread treatment with antihypertensives, it may seem problematic that the Committee recommends that the most expensive ACE inhibitors in future should not be granted reimbursement and that the general reimbursement for the angiotensin II antagonists should be limited.

Medicinal products in ATC group C09 (ACE inhibitors, angiotensin II antagonists and renin inhibitors) are, in the opinion of the Committee, however as a starting point equal treatment alternatives, and the Committee thus cannot disregard that a considerable part of the consumption of medicinal products in this ATC group, in the opinion of the Committee, is not rational. The purpose of the proposed changes is thus to encourage a more rational prescription of medicinal products in this ATC groups for the benefit of both society and the patient.

Several of the scientific societies emphasise that the patient should have access to the best possible relevant treatment, and the Danish Hypertension Society has proposed that it should be cost-neutral for the patient whether he or she is treated with one or more active substances. The Committee recognises that it varies from patient to patient whether he or she needs one or more active substances to meet the treatment targets for hypertension. The Committee is, however, at the same time of the opinion that the current needs-driven reimbursement system where the public refunding of the expenses for medicine increases with increased consumption makes adequate allowances for this proposal.

The Reimbursement Committee recommends to the Danish Medicines Agency that the consumption and prescription pattern, including the distribution between medicinal products eligible for general reimbursement and medicinal products eligible for general limited reimbursement, be continuously monitored to ensure that the limitation scheme is used as intended. To facilitate rational prescription of medicine for the doctors, it is in the opinion of the Committee important that the doctors have access to the wording of the limitation text when prescribing medicine. The Committee also recommends that the Danish Medicines Agency carefully monitor the prices of medicinal products comprised by this reassessment.

The Reimbursement Committee's viewpoints and reasons in relation to medicinal products in ATC group C02 (antihypertensives)

These medicinal products are hardly used as first-line treatment of hypertension, but primarily as a supplement to other medicinal products for the treatment of hypertension. The group comprises five substances distributed on four substance types. Two of the substances, bosentan og sitaxentan, are for hospital use only and are thus not comprised by this reassessment.

The primary use of the substance doxazosin is for the treatment of prostatic hyperplasia, and the Committee thus recommends that the reimbursement status for doxazosin first be reassessed together with medicinal products used for the treatment of prostatic hyperplasia.

The total number of patients treated in 2006 with the other medicinal products used in the primary sector, methyldopa and moxonidine, is modest: approx. 1,000 treated with methyldopa and approx. 7,000 with moxonidine. The trend for 2007 shows a small increase.

The price of treatment per day calculated in reimbursement prices is between DKK 2.48 and DKK 3.76.

The Committee is of the opinion that the medicinal products individually have a well-defined place in the therapy in combination with other antihypertensives and as such are used in a rational manner. The Committee thus recommends that the current reimbursement status be maintained for medicinal products with methyldopa and for medicinal products with moxonidine in ATC group C02.

Appendix B1 contains a detailed list of the active substances in C02 with specification of the pharmaceutical forms, names of medicinal products, approved indications for the medicinal product containing the substance in question which has been authorised for the longest period of time, dispensing terms, current reimbursement status, price of treatment per day, consumption and the Committee's specific comments on and assessment of the future reimbursement status for the medicinal products in question.

The Reimbursement Committee's viewpoints and reasons in relation to medicinal products in ATC group C03 (diuretics)

Diuretics are primarily used for the treatment of hypertension, heart insufficiency and generalised oedema. The thiazides (C03A) are preferred to the other diuretics provided their effect is adequate. Loop diuretics (C03C) are primarily used when the effect of thiazides is inadequate as well as for renal insufficiency. Potassium-sparing diuretics only have a weak diuretic effect and are therefore normally only used in combination with thiazides or loop diuretics. There is only one and no more than two substances of the individual types of diuretics.

The group of diuretics comprises many pharmaceutical forms and prices which – with the exception of eplerenon – are all in the lower end of the price scale for medicinal products for the treatment of hypertension. The price per day for oral treatment is between DKK 0.23 and DKK 3.38 (DKK 21.35 for eplerenon).

Furosemide and bendroflumethiazide with potassium account for the majority of the consumption, which the Committee finds to be rational. There is also a large consumption of spironolactone which is primarily used for the treatment of heart insufficiency.

As these medicinal products are used for several other indications than hypertension and have partially different mechanisms of action etc. and as the consumption of bumetanide is relatively low, the Committee finds the consumption of the more expensive diuretics to be rational.

The diuretics in group C03 comprise two types of combination products, one with potassium, the other with a potassium-sparing diuretic (amiloride). The primary purpose of both types is to spare potassium. In addition, there are several combination products where a diuretic is combined with a beta blocking agent, a calcium channel blocker, an ACE inhibitor or an angiotensin II antagonist. They are dealt with under the respective substance groups.

The injection fluids with furosemide and bumetanide are typically emergency service doctor products which are, however, sometimes subscribed to, e.g., patients in nursing homes who cannot ingest the substances orally, and their use is thus well-defined.

Based on an overall assessment of the group of diuretics, their application areas, the number of patients treated with the individual substances as well as the price of treatment per day for the medicinal products, the Committee is of the opinion that the consumption is rational and that there is no basis for changing the reimbursement status for these medicinal products.

Appendix B2 contains a detailed list of the active substances in C03 with specification of the pharmaceutical forms, names of medicinal products, approved indications for the medicinal product containing the substance in question which has been authorised for the longest period of time, dispensing terms, current reimbursement status, price of treatment per day, consumption and the Committee's specific comments on and assessment of the future reimbursement status for the medicinal products in question.

The Reimbursement Committee's viewpoints and reasons in relation to medicinal products in ATC group C07 (beta blocking agents)

Beta-receptor blocking drugs are used for the treatment of hypertension, angina pectoris, tachyarrhythmias, secondary prevention following myocardial infarction and heart insufficiency. In addition, the medicinal products are used for the treatment of migraine, tremor and thyreotoxicosis.

Recent studies question the role of beta blocking agents as first-line treatment in line with the other antihypertensives in the treatment of uncomplicated hypertension, and against this background several guidelines etc. (e.g. NICE, the Danish Hypertension Society[12] and the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)) have revised the recommendations for the use of beta blocking agents as first-line treatment for hypertension. The role of the substances in the treatment of ischaemic heart disease and for other indications, however, remains unchanged, and the Reimbursement Committee is of the opinion that this knowledge should not give rise to changes in the reimbursement status.

With the exception of sotalol, the different beta blocking agents are considered to be equal for the treatment of hypertension based on an assessment of effect and clinically significant adverse reactions.

The other indications of the medicinal products are not identical, and the Reimbursement Committee does not consider their use to be equal in terms of the individual indications as there are differences in effect, adverse reactions, cardioselectivity and self-stimulating effect. There is thus no evidence for extrapolation.

The price of treatment per day is between DKK 0.23 and DKK 6.88 for oral treatment. The price of treatment per day for labetalol is, however, somewhat higher (DKK 3.19 to DKK 11.52). Labetalol is the only active substance authorised for treatment of pregnant women, and the consumption figures show a rational consumption for women of child-bearing potential.

Beta blocking agents are also available as combination products with diuretics and calcium channel blockers. They are classified under the respective substance groups.

[12] http://www.hypertension.suite.dk/Guidelines.htm

The cheap substance metoprolol, the only beta blocking agent authorised for all indications, accounts for the majority of the consumption of beta blocking agents.

Based on an overall assessment of the characteristics of the beta blocking agents, their application areas, the number of patients treated with the individual substances as well as the price of treatment per day for the medicinal products, the Committee is of the opinion that the consumption of these is rational and that there is no basis for changing the reimbursement status for these medicinal products. The Committee does, however, recommend that injection fluids containing the active substances sotalol, metoprolol and labetolol in future should no be granted general reimbursement as these medicinal products, in the opinion of the Committee, are exclusively used in hospitals or, e.g., within the emergency service.

Appendix B3 contains a detailed list of the active substances in C07 with specification of the pharmaceutical forms, names of medicinal products, approved indications for the medicinal product containing the substance in question which has been authorised for the longest period of time, dispensing terms, current reimbursement status, price of treatment per day, consumption and the Committee's specific comments on and assessment of the future reimbursement status for the medicinal products in question.

The Reimbursement Committee's viewpoints and reasons in relation to medicinal products in ATC group C08 (calcium channel blockers)

The different calcium channel blockers can overall be considered to be equally effective for the treatment of uncomplicated hypertension and preventive symptomatic treatment of angina pectoris, with the exception of nimodipine which is only indicated for spasms in subarachnoidal haemorrhage. In addition, verapamil and diltiazem are used for the treatment of tachyarrhythmias, and nifedipine is also used for Raynaud's phenomenon.

In the group of dihydropyridines (C08C), amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nifedipine and nitrendipine, the price gap for oral treatment is large: DKK 0.90 to DKK 8.90 (for nimodipine: DKK 65.90). Differences in adverse reactions and interactions may, however, influence the choice of medicinal product, and in the opinion of the Reimbursement Committee the consumption of the more expensive calcium channel blockers is at a level which indicates that these medicinal products are primarily used when the cheaper ones cannot be used as only some 10 per cent of the users of dihydropyridines received the more expensive products in 2006. For the first ten months of 2007, the share was the same.

As for both verapamil and diltiazem, it is the opinion of the Committee that the consumption seems to be rational for the treatment of tachyarrhythmias, for the prevention of angina pectoris or, for verapamil, as prophylaxis following AMI when a relevant beta blocking agent is not tolerated.

It is the opinion of the Reimbursement Committee that nimodipine which is not eligible for reimbursement has found its place in the treatment for "The prevention and treatment of spasms in subarachnoidal haemorrhage caused by a burst aneurysm", and that there is no risk that it will be used outside this indication. The Committee thus recommends that nimodipine tablets be granted general unlimited reimbursement.

Only a few combination products contain calcium channel blocker. They are classified under beta blocking agents (C07), calcium channel blockers (C08) and angiotensin II antagonists (C09), respectively.

In summary, it is the opinion of the Reimbursement Committee that the use of the calcium channel blockers – the majority of the consumption being the cheaper substances amlodipine and felodipine – is appropriate and the Committee thus recommends that the calcium channel blockers maintain the current reimbursement status.

Appendix B4 contains a detailed list of the active substances in C08 with specification of the pharmaceutical forms, names of medicinal products, approved indications for the medicinal product containing the substance in question which has been authorised for the longest period of time, dispensing terms, current reimbursement status, price of treatment per day, consumption and the Committee's specific comments on and assessment of the future reimbursement status for the medicinal products in question.

The Reimbursement Committee's viewpoints in relation to medicinal products in ATC group C09 (ACE inhibitors, angiotensin II antagonists and renin inhibitors)

In the opinion of the Reimbursement Committee, there is a class effect both within the ACE inhibitors and the angiotensin II antagonists even though not all substances are as substantially documented in clinical endpoint studies. The Committee thus finds that there are no clinically relevant differences in terms of effect or adverse reactions in either group. Added to this is the recommendation that the two substance groups are equal on all indications, including also for diabetics, as appears from the recently revised guidelines from the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). A large majority of the patients can therefore be treated with the cheaper ACE inhibitors.

As for the treatment of hypertension alone, there are generally more data on ACE inhibitors than on angiotensin II antagonists. For patients with heart insufficiency, the data show no differences in effect for the treatment with ACE inhibitors or angiotensin II antagonists. For diabetics, it is recommended that type 1 diabetics with microalbuminuria be treated with an ACE inhibitor. Both ACE inhibitors and angiotensin II antagonists have a documented preventive effect on the development of nephropathy in type 2 diabetics.

For the progression of chronic renal insufficiency, ACE inhibition has a beneficial effect on diabetic nephropathy in type 1 diabetics as well as on non-diabetic nephropathy, and angiotensin II antagonist on diabetic nephropathy. At the moment, the sharp distinction between type 1 and type 2 diabetes is, however, being revised for the treatment with medicinal products from group C09, cf. the revised European guidelines.

The justification for the recommendation that the ACE inhibitors **perindopril, quinapril, benazepril, fosinopril and trandolapril** should not in future be granted general reimbursement or general limited reimbursement is the medicinal products' reimbursement price which, in the opinion of the Committee, is not considered reasonable in proportion to the treatment value when compared to the reimbursement prices for medicinal products containing the other ACE inhibitors, captopril, enalapril, lisinopril and ramipril.

In the opinion of the Reimbursement Committee, the consumption of the more expensive ACE inhibitors is not rational as it must be expected that only a very limited number of patients should be treated with these and not 22 per cent as was the case in 2006. They accounted for 56 per cent of the total expenses for the treatment with ACE inhibitors. The corresponding figures for the first ten months of 2007 are 20 per cent of the patients and 49 per cent of the expenses.

A common characteristic of the **angiontensin II antagonists** in ATC groups C09C and C09D is that these medicinal products, in the opinion of the Reimbursement Committee, do not measure up to the treatment value of the medicinal products for the large number of patients who can be treated with one of the cheaper ACE inhibitors eligible for general reimbursement. For those patients who cannot tolerate ACE inhibitors, e.g. because of cough, the price of the angiotensin II antagonists will, in the opinion of the Committee, to a larger extent measure up to the treatment value, and the Committee thus recommends that the reimbursement be limited to exactly these patients.

Figures from the Danish Medicines Agency's Register of Medicinal Product Statistics show that in 2006 at total of 476,332 patients were being treated with ACE inhibitors and/or angiotensin II antagonists. Of these, 199,803, corresponding to 42 per cent, were being treated with an angiotensin II antagonist. In the first ten months of 2007, 508,312 persons were being treated with ACE inhibitors and/or angiotensin II antagonists. Of these, 216,089, corresponding to 43 per cent, were being treated with an angiotensin II antagonist. It is normally assumed that 5 to 20 per cent[13] of patients treated with ACE inhibitors have adverse reactions in the form of cough. The 42 to 43 per cent thus suggest that the consumption of angiotensin II antagonists is not rational. This is supported by a survey conducted by the Danish Medicines Agency which shows that for 46 per cent of the patients who in 2006 started a treatment with an angiotensin II antagonist no prior treatment had been attempted with an ACE inhibitor[14]. The figure for the first three quarters of 2007 is also 46 per cent, and against this background the Committee does not find the consumption to be rational.

The purpose of the proposed limited reimbursement for medicinal products containing the **angiotensin II antagonists losartan, eprosartan, valsartan, irbesartan, candesartan, telmisartan and olmesartan** is to encourage the use of the cheaper ACE inhibitors eligible for general reimbursement where possible.

The Reimbursement Committee is of the opinion that by removing the reimbursement for the more expensive ACE inhibitors in ATC groups C09A and C09B and by limiting the reimbursement for the angiotensin II antagonists in ATC groups C09C and C09D, you support rational pharmacotherapy and encourage the doctors, as a starting point, to use the cheaper ACE inhibitors eligible for general reimbursement.

The new substance **aliskiren** in ATC group C09X represents a new mechanism of action within the renin-angiotensin system compared to the mechanisms of action for the ACE inhibitors and angiotensin II antagonists which inhibit other stages in the same system. The price of aliskiren is at the same level as the angiotensin II antagonists.

The place of aliskiren in the treatment of hypertension should, in the opinion of the Committee, be reserved to patients with mild to medium uncomplicated hypertension where the treatment targets cannot be met using other antihypertensives[15], and aliskiren is thus not first-line treatment.

[13] www.Medicin.dk (in Danish only)
[14] http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=6434
[15] http://www.irf.dk/en/reviews/rasilez_aliskiren.htm

Against this background, the Reimbursement Committee is of the opinion that the reimbursement for aliskiren should be limited like the angiotensin II antagonists.

Appendix B5 contains a detailed list of the active substances in C09 with specification of the pharmaceutical forms, names of medicinal products, approved indications for the medicinal product containing the substance in question which has been authorised for the longest period of time, dispensing terms, current reimbursement status, price of treatment per day, consumption and the Committee's specific comments on and assessment of the future reimbursement status for the medicinal products in question.

The Committee's conclusions

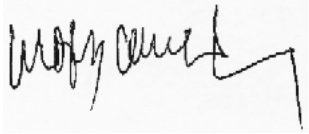
The large majority of the medicinal products which are authorised for the treatment of cardiovascular diseases in Denmark are today granted general reimbursement, and the Committee recommends to the Danish Medicines Agency that practically all medicinal products in ATC groups C02 (antihypertensives), C03 (diuretics), C07 (beta blocking agents) and C08 (calcium channel blockers) maintain the general reimbursement status. It is the opinion of the Committee that the use of these medicinal products is generally rational and that the public funding for reimbursement for these medicinal products is thus also used in an expedient manner. In addition, one medicinal product (nimodipine), which is not granted general reimbursement today, is recommended for general reimbursement.

In the opinion of the Committee, medicinal products in ATC group C09 (ACE inhibitors, angiotensin II antagonists and renin inhibitors) do, however, differ from the other medicinal products and are, to a certain extent, not used rationally. The most expensive of these medicinal products should not be first-line agents in treatment with substances affecting the renin angiotensin system. The Committee thus recommends that the most expensive ACE inhibitor no longer be granted general reimbursement and that the general reimbursement for angiotensin II antagonists be limited to patients who cannot be treated with cheaper medicinal products in ATC group C09 eligible for reimbursement.

The Committee recommends to the Danish Medicines Agency that the consumption and prescription pattern, including the distribution between medicinal products eligible for general reimbursement and medicinal products eligible for general limited reimbursement, be continuously monitored to ensure that the limitation scheme is used as intended.

Should the Danish Medicines Agency elect to follow the Reimbursement Committee's recommendation that certain medicinal products in ATC group C09 should no longer be granted general reimbursement, and that the reimbursement for other medicinal products which today are granted general reimbursement should be limited, the Reimbursement Committee requests the Danish Medicines Agency to plan these changes in such a way that patients and doctors are given a period of notice appropriately long to reschedule the treatment of the patients to the cheaper treatment alternatives eligible for general reimbursement.

On behalf of the Committee



Mogens Laue Friis
Chairman

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Consultation answers from scientific societies

- Danish Society of Internal Medicine dated 27 November 2006
- Danish College of General Practitioners dated 8 October 2006
- Danish Society of Nephrology dated 10 August 2006
- Danish Society of Cardiology dated 16 June 2006
- Danish Hypertension Society dated 9 May 2006
- Danish Endocrine Society dated 4 April 2006
- Danish Medical Society dated 28 March 2006

(www.laegemiddelstyrelsen > Companies > General reimbursement > Reassessment of reimbursement status for medicinal products (announcement of 15 December 2006): http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=10459

Replies from patient groups

- Danish Stroke Association dated 16 September 2005
- Danish Heart Foundation dated 24 August 2005
- Danish Diabetes Association dated 23 August 2005

(www.laegemiddelstyrelsen > Companies > General reimbursement > Reassessment of reimbursement status for medicinal products (announcement of 15 December 2006): http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=10459

Appendices

A1	Graphic overview of ATC group C02, antihypertensives
A2	Graphic overview of ATC group C03, diuretics
A3	Graphic overview of ATC group C07, beta blocking agents
A4	Graphic overview of ATC group C08, calcium channel blockers
A5	Graphic overview of ATC group C09, ACE inhibitors, angiotensin II antagonists and renin inhibitors
B1	Overview of the Reimbursement Committee's comments on and recommendation for the reimbursement status for the individual active substances and pharmaceutical forms in C02, antihypertensives
B2	Overview of the Reimbursement Committee's comments on and recommendation for the reimbursement status for the individual active substances and pharmaceutical forms in C03, diuretics
B3	Overview of the Reimbursement Committee's comments on and recommendation for the reimbursement status for the individual active substances and pharmaceutical forms in C07, beta blocking agents
B4	Overview of the Reimbursement Committee's comments on and recommendation for the reimbursement status for the individual active substances and pharmaceutical forms in C08, calcium channel blockers
B5	Overview of the Reimbursement Committee's comments on and recommendation for the reimbursement status for the individual active substances and pharmaceutical forms in C09, ACE inhibitors, angiotensin II antagonists and renin inhibitors
C1	Price survey for active substances and pharmaceutical forms in C02, antihypertensives, for six price periods (for the period 22 October to 31 December 2007)
C2	Price survey for active substances and pharmaceutical forms in C03, diuretics, for six price periods (for the period 22 October to 31 December 2007)
C3	Price survey for active substances and pharmaceutical forms in C07, beta blocking agents, for six price periods (for the period 22 October to 31 December 2007)
C4	Price survey for active substances and pharmaceutical forms in C08, calcium channel blockers, for six price periods (for the period 22 October to 31 December 2007)
C5	Price survey for active substances and pharmaceutical forms in C09, ACE inhibitors, angiotensin II antagonists and renin inhibitors, for six price periods (for the period 22 October to 31 December 2007)
D	Explanation to how the price surveys are structured, Appendices C1-C5