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

The Danish Medicines Agency has submitted the Reimbursement Committee's recommendation of 29 January 2008 concerning the future reimbursement status of medicinal products for cardiovascular diseases in ATC groups C02, C03, C07, C08 and C09 (blood pressure medication) for consultation. The consultation deadline was 5 May 2008.

The Danish Medicines Agency has received seven consultation responses from affected companies, nine contributions from scientific societies, four from patient organisations and four from others. A list of the consultation responses (in Danish only) has been published at the Danish Medicines Agency's website.

The Reimbursement Committee has been presented with all responses, which have been discussed at the Committee meetings held on 20 May 2008, 17 June 2008 and 26 August 2008.

Based on the responses received, the Committee has decided to propose an amended reimbursement condition for medicinal products comprised by item 9 in the Reimbursement Committee's recommendation of 29 January 2008, see below.

The Committee has not assessed any changes in price and consumption that have occurred after the recommendation of 29 January 2008, but the Committee presupposes that the Danish Medicines Agency in its decision will assess any such changes and their influence on the Danish Medicines Agency's decision.

Apart from the above, the Committee maintains its recommendation of 29 January 2008.

Below is a copy of the Reimbursement Committee's full recommendation for medicinal products in ATC groups C02, C03, C07, C08 and C09 with the amended reimbursement condition in item 9. This is followed by the Committee's comments to a number of issues raised in the consultation responses along with the Committee's reasons for amending the reimbursement condition.

The Reimbursement Committee's recommendation

The Reimbursement Committee recommends to the Danish Medicines Agency that:

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

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

the individual substances: sotalol, metoprolol and labetalol

[1] 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).

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 eligible for general or general conditional 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 eligible for general or general conditional reimbursement.

9.
All medicinal products in ATC groups C09C and C09D (angiotensin II antagonists) and C09X (other agents acting on the renin-angiotensin system) 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 conditional reimbursement with the following reimbursement condition:

> "Patients with hypertension or any other type of cardiovascular disease requiring treatment, where treatment with less expensive medicinal products acting on the renin-angiotensin system that are eligible for general reimbursement
> - has proven inadequate or is not tolerated, or
> - in exceptional cases has been deemed inappropriate by a doctor based on an overall clinical assessment of the patient's condition."

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

Reasons and comments on consultation response

The submitted consultation responses touch upon a range of issues which the Committee would like to comment on. The issues are:

- Class effect in the group of ACE inhibitors and the group of angiotensin II antagonists
- Choice of ACE inhibitors versus choice of angiotensin II antagonists
- Objections against product switch
- Amendment of the proposed reimbursement condition for angiotensin II antagonists
- Undertreatment relative to the proposed reimbursement amendments
- Economics

Class effect in the group of ACE inhibitors and the group of angiotensin II antagonists
In its recommendation of 29 January 2008, the Committee has taken the view that there is a class effect in the group of ACE inhibitors and in the group of angiotensin II antagonists. This is disputed in several of the consultation responses.

The concept 'class effect' is commonly used in treatment guidelines, clinical guidelines, etc. and it refers to the comparable therapeutic effect(s) and adverse reactions of a number analogous substances, regardless that the documentation for the individual substances varies. The class effect of a group of analogous products is rarely documented, but it is based on randomised studies of several medicines in the same analogous group and on the resemblance between the chemical structures and mechanisms of action of the substances.

The consultation responses refer to a number of studies, each of which documents the properties of individual substances in the treatment of specific patient groups. However, it is the opinion of the Committee that if pharmacological and kinetic aspects are to be used as arguments in favour of choosing

one substance over other analogous substances, then it must be proven that there are *clinically significant* benefits of this particular substance. This is not documented by the studies. Experience from everyday clinical practice is one of the aspects considered when the reimbursement status of a medicinal product is to be reassessed.

In the group of ACE inhibitors and in the group of angiotensin II antagonists, the Committee does not find that there is a basis for distinguishing between individual substances for the treatment of the large group of hypertensive patients in everyday clinical use, although exceptional cases may warrant the selection of a specific ACE inhibitor or a specific angiotensin II antagonist. The currently suggested reimbursement condition for angiotensin II antagonists takes this actuality into account.

Likewise, some consultation responses state that differences in the authorised indications warrant a difference in reimbursement status. The Committee has made an individual assessment of each individual medicinal product and has also considered the authorised indications, cf. appendix B5 in the recommendation of 29 January 2008. Referring to the class effect and the clinical experience, the Committee does not, however, find that differences in the authorised indications justify a difference in reimbursement status.

The consultation responses state that captopril, which must be administered several times a day, is not an appropriate treatment. The Committee agrees that antihypertensive treatment with a single daily dose is the preferred choice, but it maintains its recommendation that captopril should remain eligible for general reimbursement, as the number of persons treated decreased by 44 per cent from 2003 to 2007, and the Committee expects this development to continue. Moreover, new patients would probably not be started on treatment with captopril.

Choice of ACE inhibitors versus choice of angiotensin II antagonists
Several of the consultation responses question the fact that the Reimbursement Committee in its recommendation of 29 January 2008 generally ranks the therapeutic value of ACE inhibitors alongside angiotensin II antagonists, and that the Committee therefore with reference to price considers the less expensive ACE inhibitors to be the most clinically rational choice in the majority of cases.

In the grounds for its recommendation, the Committee has attached great importance to the fact that the newest European guidelines dealing with treatment of hypertension do not distinguish between ACE inhibitors and angiotensin II antagonists. In general, the recommended treatment is “ACE inhibitor/angiotensin II antagonist” or “treatment with an ACE inhibitor or angiotensin II antagonist”. However, there may still be some cases where the one type may be preferred over the other, or cases where a combination of an ACE inhibitor and an angiotensin II antagonist may be required, but it is the opinion of the Committee that in everyday clinical practice, there is no scientifically relevant basis for distinguishing between these two groups of medicinal products.

The responses received refer to certain therapeutic indications (type 2 diabetics with nephropathy and patients with left ventricular hypertrophy) for which the evidence of efficacy is demonstrated for angiotensin II antagonists only.

It is correct that previously, only angiotensin II antagonists showed evidence of efficacy for the treatment and prevention of nephropathy in patients with type 2 diabetes. However, new studies[2]

[2] Also including ONTARGET from 2008: ONTARGET Investigators, Yusuf S, Teo KK, Pogue J et al. Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events. N Engl J Med 2008;358:1547-59 (http://content.nejm.org/cgi/content/full/358/15/1547).

suggest that the efficacy of ACE inhibitors is equal to angiotensin II antagonists for the treatment and reduction of progression of nephropathy in patients with type 2 diabetes and the prevention of cardiovascular events in high risk groups. These data are reflected in the new European guidelines[3] which indicate that it is possible to choose freely between ACE inhibitors and angiotensin II antagonists with respect to diabetics.

Efficacy of both angiotensin II antagonists and ACE inhibitors in reduction of left ventricular hypertrophy in hypertensive patients has been demonstrated. Only a few studies have compared angiotensin II antagonists and ACE inhibitors with respect to this effect, finding them to apparently have equal effect. The newest European guidelines make no distinction between ACE inhibitors and angiotensin II antagonists for the treatment of patients with left ventricular hypertrophy.

Objections against product switch
Some consultation responses state that switching to another product may imply that patients during the transitional period will not be adequately controlled, thereby increasing the risk of cardiovascular events. The consultation responses refer to a study from 2004, VALUE[4].

The Committee does not find that the product switches which the proposed reimbursement amendment might give rise to will put patients at increased risk in general. The recommended amended condition for general reimbursement of angiotensin II antagonists, cf. above, now takes into consideration exceptional cases where the doctor finds – based on an overall clinical assessment of the patient's condition – that it would be inappropriate to change the patient's treatment.

VALUE is a randomised, double-blind multi-centre study of 15,245 high risk patients conducted with the purpose of comparing a valsartan-based regimen with an amlodipine-based regimen over a mean period of 4.2 years from the first cardiac event, the presumption being that valsartan has benefits over amlodipine at the same blood pressure reduction.

However, the consultation responses use the VALUE study to substantiate the risk feared to be present if well-controlled hypertension patients switch from an angiotensin II antagonist to an ACE inhibitor.

The VALUE study gives rise to the suspicion that discontinuing all antihypertensive drugs in hypertension patients at high cardiovascular risk and resuming new treatment, where it takes about three to six months to control the blood pressure, will lead to more cardiac events in a valsartan-based regimen than in an amlodipine-based regimen. Many of the consultation responses interpret this suspicion to mean that a possible change from an angiotensin II antagonist to an ACE inhibitor in well-controlled hypertension patients will imply a similarly increased risk.

However, in the opinion of the Committee, several aspects go against this extrapolation, e.g. the fact that the patients were primarily switched from an ACE inhibitor to an angiotensin II antagonist and not the other way around, and the fact that, in general, the test subjects were not well-controlled. It is also

[3] 2007 guidelines for the management of arterial hypertension. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J. Hypertension vol. 25(6):1105-1187, June 2007 (http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/arterial-hypertension.aspx).
[4] Julius S, Kjeldsen SE, Weber M et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: The VALUE randomised trial. Lancet 2004; 363: 2022-31 (http://www.thelancet.com/journals/lancet/article/PIIS0140673604164519/abstract).

essential that the purpose of the VALUE study was not to investigate the potential risk associated with the crossover from an angiotensin II antagonist to an ACE inhibitor and therefore it is not tailored to the purpose.

The Committee also found reason to point out that any product switch should always take place gradually, which was not the case in the VALUE study, and under close supervision.

Amendment of the proposed reimbursement condition for angiotensin II antagonists
Several parties have proposed that it should be up to the treating doctor to assess whether or not it would be appropriate to switch the patient to another treatment, and that the reimbursement condition for angiotensin II antagonists proposed in the Committee's recommendation of 29 January 2008 should therefore be softened accordingly.

The Reimbursement Committee agrees that if a doctor *in exceptional cases* concludes, based on an overall clinical assessment of a patient's condition, that it would be inappropriate to treat the patient with a less expensive medicinal product acting on the renin-angiotensin system that is eligible for general reimbursement, no such switch should take place. Likewise, there may also be exceptional cases where it would be rational to start a patient on treatment with an angiotensin II antagonist without prior treatment with an ACE inhibitor.

The Reimbursement Committee therefore recommends that the proposed reimbursement condition be amended.

Undertreatment relative to the proposed reimbursement amendments
Several of the consultation responses have stressed the need for making special efforts to eliminate undertreatment in the hypertension area, raising concerns that the Committee's proposed changes to the reimbursement status of antihypertensives might lead to further undertreatment in Denmark. As stated in the recommendation of 29 January 2008, the Committee recognises the issue of undertreatment, which exists despite the fact that antihypertensives have always been eligible for general reimbursement. The Committee shares the view that there is a need to increase the focus on eliminating undertreatment.

However, the Committee does not find that the proposed amendments go against ameliorating the issue of undertreatment, since the proposed amendments comply with the current treatment recommendations and rational pharmacotherapy.

If the Danish Medicines Agency accepts the Committee's recommendation according to which the most expensive ACE inhibitors will no longer be eligible for general reimbursement and angiotensin II antagonists will be eligible for general conditional reimbursement, there will still be a wide range of medicinal products in these ATC groups eligible for general or general conditional reimbursement.

Statistically, about one fourth of hypertensive patients are not adequately controlled. The Reimbursement Committee believes that an increased focus on these patients in connection with a switch to another medicine will better the control issue and ensure a greater extent of adequate treatment. In addition, it is likely that lower treatment expenses resulting from a product switch will improve the patient's compliance.

Economics

At the request of the Danish Medicines Agency and as part of the periodic reassessment process introduced by the Danish Health Act, which entered into force in April 2005, the Committee has assessed the therapeutic value of the above medicinal products relative to their price with a view to making a recommendation about their future reimbursement status.

With the proposed amendments relative to the current reimbursement status, the Committee is of the opinion that the medicinal products in the ATC groups concerned will be provided with a reimbursement status as entitled by their efficacy – and other aspects – judged from the perspective of rational pharmacotherapy. The probability that the proposal may imply reduced expenses for the public sector and the patient alike is an added bonus.

A number of the consultation responses has pointed out that switching patients from one medicine to another may lead to an increase in required checkups. The Committee is of the opinion that a switch to another product could take place in connection with these patients' regular control visits to their doctor, but it recognises that a product switch would typically necessitate extra visits to the doctor for the individual patient. However, considering that the medicinal product which the patient is expected to be switched to is considerably less expensive compared with the product that the patient is currently taking, and considering that the treatment is often lifelong, the Committee estimates that the additional expenses resulting from such a switch would be regained quickly.

On behalf of the Committee

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Chairman