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DANISH MEDICINES AGENCY

Reassessment of reimbursement status for lipid-lowering medicines, ATC Group C10

March, 16 2007

Journal no:
5315-8
Our ref: Lipid Reassessment.
Decision.b.160307

Introduction

By the end of 2004[1], the Danish Parliament decided that decisions on general reimbursement for medicinal products should be subject to periodic reassessment.

The reassessment aims at assessing whether the assumptions underlying the original decision on granting or not granting general, including restricted, reimbursement, are still valid.

The Danish Medicines Agency is currently reassessing the reimbursement status of all medicinal products over a period of five years, and the below decisions will conclude the reassessment of the reimbursement status of lipid-lowering medicines (ATC Group C10).

The decisions and accompanying justifications are directed towards companies with medicinal products in the indicated ATC groups with marketing authorisations in Denmark on 15 March 2007.

We enclose an appendix with a list of the medicinal products from your company which the decision concerns.

The decisions entail an overall relaxation of the reimbursement status of lipid-lowering medicines and will support treatment with lipid-lowering medicines when the patient suffers from hyperlipidemia requiring medication therapy and will encourage the use of the cheaper statins which are eligible for general reimbursement, where possible, alone or in combination with one of the other lipid-lowering substances.

[1] In connection with the adoption of Act no. 1431 of 22 December 2004 on Amendment of the Act on National Health Insurance. The amendment entered into force on 1 January 2005. The Act on National Health Insurance was replaced by the Danish Health Care Act; Act no. 546 of 24 June 2005. The reassessment rules remain unchanged under the Health Care Act.

This decision is presented as a collective decision on the reimbursement status of all lipid-lowering medicines (ATC Group C10). It should be emphasised, however, that the Danish Medicines Agency has carried out a specific assessment of all medicines covered by the reassessment, including all products included in the attached list of your company's medicinal products.

As an introduction, the decisions made, with accompanying justifications, are outlined below, followed by general remarks on consumption and consumption developments, quotes from the legal basis, presentation of the case and complaints guidance.

1. General reimbursement

(*simvastatin, lovastatin and pravastatin*)

Decision

Effective from 23 April 2007, the Danish Medicines Agency grants general reimbursement without restriction for all medicinal products with marketing authorisations in Denmark on 15 March 2007 that contain one of the following statins (C10AA):

- C10AA01: Simvastatin
- C10AA02: Lovastatin
- C10AA03: Pravastatin

Justification

This decision was based on Section 144 (1) of the Danish Health Care Act, cf. Section 1 (1) and (2) of the Executive Order on Reimbursement[2].

For the sake of good order, it is emphasised that the decision is not directed towards medicinal products containing the statins mentioned above, which are not classified in ATC group C10AA, e.g. combination products, cf. below.

In reaching the decision, we have emphasised the fact that medicinal products containing the statins *simvastatin, lovastatin and pravastatin* are all useful first choices in the treatment of most hyperlipidemia cases.

In our clinical evaluation of the medicinal products, we have given emphasis to the Danish Society of Cardiology's clinical guidelines for the prevention of cardiovascular diseases[3], the recommendations and

[2] Executive Order no. 180 of 17 March 2005 on reimbursement of medicinal products.

[3] The interdisciplinary task group for prevention of cardiovascular disease in Denmark established by the Danish Society of Cardiology. Clinical guidelines on the prevention of cardiovascular disease in Denmark ("*Kliniske retningslinier for forebyggelse af*

background notes on lipid-lowering medicines by the Institute for Rational Pharmacotherapy[4], and NICE's technological evaluation of statins[5] supplemented by the SPARCL study[6] published subsequently.

This is described in more detail in the Reimbursement Committee's recommendation of 7 September 2006, to which we refer.

Furthermore, we have attached importance to the fact that the average lowest daily treatment price in the period 22 May 2006 – 31 July 2006 was between DKK 0.91 and DKK 3.26 for these medicinal products.

The Reimbursement Committee's recommendation of 7 September 2006 includes an account of the prices and doses on which the Reimbursement Committee's recommendation for the reimbursement status of the medicines was based. We refer to the information stated by the Reimbursement Committee. The prices and price level developments since then do not justify a change of the assessment.

On this background, the Danish Medicines Agency assesses that the reimbursement prices of these medicines are reasonable compared to the therapeutic value of the products.

Reference is further made to the details indicated below on the consumption and consumption development as well as our comments to the consultation responses received.

2. Restricted reimbursement
(*fluvastatin, atorvastatin, rosuvastatin, cholestyramine, colestipol, acipimox, ezetimibe and combination of simvastatin and ezetimibe*)

Decision

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kardiovaskulær sygdom i Danmark"). Danish Society of Cardiology, 2004 (www.cardio.dk).

[4] Institute for Rational Pharmacotherapy. Lipid-lowering medicinal products – Recommendations and background notes ("*Lipidsænkende lægemidler - Rekommandationer og baggrundsnotater*"). Institute for Rational Pharmacotherapy, 2005 (www.irf.dk).

[5] National Institute for Health and Clinical Excellence (NICE). Statins for the prevention of cardiovascular events. Technology Appraisal 94. NICE, 2006 (www.nice.org).

[6] SPARCL investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Eng J Med 2006; 355: 549-59.

Effective from 23 April 2007, the Danish Medicines Agency grants restricted reimbursement for all medicinal products with marketing authorisations in Denmark on 15 March 2007 that contain one of the following substances:

- C10AA04: Fluvastatin
- C10AA05: Atorvastatin
- C10AA07: Rosuvastatin
- C10AC01: Cholestyramine
- C10AC02: Colestipol
- C10AD06: Acipimox
- C10AX09: Ezetimibe
- C10BA02: Combination of simvastatin and ezetimibe

General reimbursement for these medicinal products is restricted for:

> "Patients with hyperlipidemia necessitating treatment for whom therapy with statins eligible for general reimbursement without restriction has proved insufficient or who do not tolerate these medicines."

Justification
This decision was based on Section 144 (1) of the Danish Health Care Act, cf. Section 1 (1), (2) and (4) of the Executive Order on Reimbursement.

Reimbursement for medicinal products subject to restricted reimbursement is conditional on the doctor endorsing the prescription with "reimbursement" ("*tilskud*"), cf. Section 1 (4) of the Executive Order on Reimbursement.

The Danish Medicines Agency assesses that the effect of the statins is largely a class effect, and the decision to grant restricted reimbursement for fluvastatin, atorvastatin and rosuvastatin is therefore justified by the reimbursement prices of the medicinal products, cf. below.

The Danish Medicines Agency assesses that medicinal products containing the anion exchangers *colestipol and cholestyramine* and the nicotinic acid derivative *acipimox* each have their place in the therapy, mainly as a supplement to statins.

We have attached importance to the consumption data for the more recent *ezetimibe* which indicates that the substance is primarily used as a supplement to statins and not as first-choice therapy for hyperlipidemia necessitating treatment. However, the Danish Medicines Agency will carefully follow developments in the consumption of this substance.

As far as the *combination of simvastatin and ezetimibe* is concerned, it is assessed that in the cases where both substances are needed, the combination may result in better compliance than if the substances are administered individually. However, treatment with a cheaper statin alone is the first-line regimen for patients with hyperlipidemia necessitating treatment, and we will therefore follow the consumption developments carefully.

In our clinical evaluation of the medicinal products, we have given emphasis to the Danish Society of Cardiology's clinical guidelines for the prevention of cardiovascular diseases[7], the recommendations and background notes on lipid-lowering medicines by the Institute for Rational Pharmacotherapy[8], and NICE's technological evaluation of statins[9] supplemented by the SPARCL study[10] published subsequently.

This is described in more detail in the Reimbursement Committee's recommendation of 7 September 2006, to which we refer.

We have attached importance to the fact that the average lowest daily treatment price in the period 22 May 2006 – 31 July 2006 was between DKK 8.50 and DKK 24.32 for these medicines.

By way of comparison, the average lowest treatment price for simvastatin, lovastatin and pravastatin was between DKK 0.91 and DKK 3.26.

The Reimbursement Committee's recommendation of 7 September 2006 includes an account of the prices and doses on which the Reimbursement Committee's recommendation for the reimbursement status of the medicines was based. The Danish Medicines Agency refers to the information stated by the Reimbursement Committee. The prices and price level developments since then do not justify a change of the assessment.

It is our assessment that for the large group of patients who can receive treatment solely with, or based on, one of the statins for which general

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[7] The interdisciplinary task group for prevention of cardiovascular disease in Denmark established by the Danish Society of Cardiology. Clinical guidelines on the prevention of cardiovascular disease in Denmark ("*Kliniske retningslinier for forebyggelse af kardiovaskulær sygdom i Danmark*"). Danish Society of Cardiology, 2004 (www.cardio.dk).

[8] Institute for Rational Pharmacotherapy. Lipid-lowering medicinal products – Recommendations and background notes ("*Lipidsænkende lægemidler - Rekommandationer og baggrundsnotater*"). Institute for Rational Pharmacotherapy, 2005 (www.irf.dk).

[9] National Institute for Health and Clinical Excellence (NICE). Statins for the prevention of cardiovascular events. Technology Appraisal 94. NICE, 2006 (www.nice.org).

[10] SPARCL investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Eng J Med 2006; 355: 549-59.

reimbursement without restriction has been granted, the reimbursement prices of the medicinal products listed above are not reasonable compared to the therapeutic value.

For patients with hyperlipidemia necessitating treatment, in whom therapy with the statins eligible for general reimbursement without restriction has proved insufficient, or who do not tolerate these medicines, it is our assessment that the reimbursement prices of the mentioned medicinal products are reasonable compared to their therapeutic value.

Reference is further made to the below information on the consumption and consumption development as well as our comments to the consultation responses received.

3. Restricted reimbursement
(*fibrate*)

Decision
Effective from 23 April 2007, the Danish Medicines Agency grants restricted reimbursement for all medicinal products with marketing authorisations in Denmark on 15 March 2007 that contain the fibrate:

- C10AB04: Gemfibrozil

General reimbursement for these medicinal products is restricted for:

> "Patients with isolated, severely elevated triglycerides or patients with combined hyperlipidemia, possibly combined with statin."

Justification
The decision was based on Section 144 (1) of the Danish Health Care Act, cf. Section 1 (1), (2) and (4) of the Executive Order on Reimbursement.

Reimbursement for medicinal products subject to restricted reimbursement is conditional on the doctor endorsing the prescription with "reimbursement" ("*tilskud*"), cf. Section 1 (4) of the Executive Order on Reimbursement.

We have emphasised the fact that medicinal products containing the statins *simvastatin, lovastatin and pravastatin* should be used as first choice treatment of most cases of hyperlipidemia, cf. above, but that gemfibrozil should be used as first choice for isolated, severely elevated triglycerides and in case of combined hyperlipidemia.

In our clinical evaluation, we have given emphasis to the Danish Society of Cardiology's clinical guidelines for the prevention of cardiovascular

disease[11], and the recommendations and background notes on lipid-lowering medicines by the Institute for Rational Pharmacotherapy[12].

This is described in more detail in the Reimbursement Committee's recommendation of 7 September 2006, to which we refer.

Furthermore, we have attached importance to the fact that the average lowest daily treatment price in the period 22 May 2006 – 31 July 2006 was DKK 9.22 for this medicinal product. The prices and price level developments since then do not justify a change of the assessment.

It is our assessment that for the large group of patients who can receive treatment solely with, or based on, one of the statins for which general reimbursement without restriction has been granted, the reimbursement prices of medicinal products containing the fibrate gemfibrozil are not reasonable compared to the therapeutic value.

However, we believe that the reimbursement prices of the medicinal products containing the fibrate gemfibrozil are reasonable compared to the therapeutic value when treating patients with isolated severely increased triglycerides or patients with combined hyperlipidemia, possibly in combination with statin.

Reference is further made to the below information on the consumption and consumption development as well as our comments to the consultation responses received.

Consumption data for lipid-lowering medicines

The decision by the Danish Medicines Agency on the reimbursement status for the lipid-lowering medicines relies on information about consumption and turnover of lipid-lowering medicines and the number of people receiving treatment with these medicines in the years 2001-2005. Preliminary consumption figures and the developments in consumption in 2006 do not justify a change of the evaluation.

In 2005, 307,000 individuals received treatment with medicinal products from ATC group C10 – of whom 303,400, corresponding to 99 percent,

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[11] The interdisciplinary task group for prevention of cardiovascular disease in Denmark established by the Danish Society of Cardiology. Clinical guidelines on the prevention of cardiovascular disease in Denmark ("*Kliniske retningslinier for forebyggelse af kardiovaskulær sygdom i Danmark*"). Danish Society of Cardiology, 2004 (www.cardio.dk).

[12] Institute for Rational Pharmacotherapy. Lipid-lowering medicinal products – Recommendations and background notes ("*Lipidsænkende lægemidler - Rekommandationer og baggrundsnotater*"). Institute for Rational Pharmacotherapy, 2005 (www.irf.dk).

received statin treatment. Almost 15 percent of statin-treated patients received the more expensive statins (atorvastatin, rosuvastatin and fluvastatin). The expenses for these three medicinal products accounted for 65 percent of the total expenses for statins.

There are patients in whom the use of expensive statins is rational. This applies, for instance, to patients whose cholesterol levels could not be reduced by the use of, e.g., simvastatin, pravastatin or lovastatin.

Part of the consumption of the more expensive statins appears not to be rational, however. This is partly because 41 percent of the consumption of atorvastatin is at the 10 mg strength, and it must be assumed that a substantial number of patients could achieve the same lipid reduction by using simvastatin 40 mg, and partly because 31 percent of the new atorvastatin users in 2005 (1,779 of 5,725) did not receive immediately prior simvastatin treatment. On the other hand, developments in recent years would appear to indicate a reduction in the consumption of atorvastatin.

The total consumption over the last five years of the four types of lipid-lowering medicines; statins, fibrates, anion exchangers and nicotinic acid derivatives, shows that the increase is solely attributable to statins, which is a rational development.

As concerns ezetimibe, extracts from the Register of Medicinal Product Statistics at the Danish Medicines Agency show that some 900 individuals bought ezetimibe at least once in 2005. Of these, 80 percent bought a statin product at least once in the same period, while 20 percent did not buy a statin product in this period.

We assess that there is presumably a basis for converting part of the consumption to the more inexpensive statins that are eligible for general reimbursement and continuing to encourage initial treatment with those statins.

The Danish Medicines Agency will carefully monitor the consumption of lipid-lowering medicines, including the distribution between the medicinal products eligible for general reimbursement without restriction and the medicinal products subject to restricted reimbursement.

Legal framework

The following are quotes from the provisions referred to in the above decisions.

Section 144 (1) of the Danish Health Care Act states the following:

”Reimbursement is granted for purchases of prescription-only medicinal products that have been granted general reimbursement by the Danish Medicines Agency.”

Section 1 (1), (2) and (4) of the Executive Order on Reimbursement states the following:

”Section 1. In pursuance of Section 7 (1)-(5) of the Danish National Health Security Act, the Danish Medicines Agency decides whether the national health security shall grant general, including restricted, reimbursement for the purchase of a medicinal product.

(2). When assessing whether a general reimbursement shall be granted for a medicinal product, the Danish Medicines Agency emphasises
1) whether the medicinal product has a safe and valuable therapeutic effect on a well-defined indication, and
2) whether the relationship between the price of the medicinal product and its treatment value is reasonable, see (3) and (4), however.”

(4). Pursuant to the criteria established in (2) and (3) above, The Danish Medicines Agency may decide that the national Health Security reimbursement be conditional on the medicinal product being prescribed with a view to treating specific diseases (restricted reimbursement)…”

Presentation of the case

Decision to initiate reassessment
The Danish Medicines Agency initiated the reassessment of the reimbursement status of lipid-lowering medicines (ATC Group C10) in March 2006.

At its meetings on 22 March, 25 April, 13 June and 22 August 2006, the Reimbursement Committee discussed the reimbursement status of lipid-lowering medicines at the request of the Danish Medicines Agency.

The Reimbursement Committee’s recommendation on the reimbursement status was ready on 7 September 2006.

On this background, the Danish Medicines Agency decided to initiate procedures concerning changes of the reimbursement status for the lipid-lowering medicines that were comprised by the reassessment, i.e. authorised as at 7 August 2006, including your company’s authorised lipid-lowering medicines.

Consultation
In a letter dated 29 September 2006, we asked you to submit any comments to the recommendation of the Reimbursement Committee before 20 December 2006.

Concurrently, the following other stakeholders were consulted about the Committee's recommendation:

- Other companies with authorised lipid-lowering medicines (ATC Group C10)
- Danish Society of Cardiology
- Danish Medical Society
- Danish College of General Practitioners
- Danish Society of Internal Medicine
- Danish Society for Clinical Pharmacology
- Patient Forum
- The Danish National Board of Health

We received responses from:

- AstraZeneca A/S
- Danish College of General Practitioners
- Merck Sharp & Dohme
- Pfizer ApS
- The Danish National Board of Health

The consultation responses received were presented to the Reimbursement Committee at its meeting on 16 January 2007. The Committee maintained its recommendation of 7 September 2006 with the accompanying justifications.

The consultation responses (in Danish only), the recommendation of the Reimbursement Committee and the Danish Medicines Agency's letter about the consultation have been published at the Agency's website (www.dkma.dk – cf. "news", notice of 15 February 2007).

The Danish Medicines Agency's comments to the consultation responses
Two of the consultation responses voice concerns about the unilateral focus on the price of the medicinal products in the reimbursement assessment.

It is an absolutely fundamental criterion in the assessment of the reimbursement status of medicinal products that the price of the product must be reasonable compared with its therapeutic value. The assessment as to whether this criterion has been fulfilled thus requires careful

consideration of the therapeutic value of the medicinal product and knowledge of its price.

Accordingly, the comments for the amendment of the Danish Health Security Act by Act no. 1045 of 23 December 1998, which introduced the current criteria for granting reimbursement, include the following statement:

> ”In connection with authorising a medicinal product, it cannot be required that a medicinal product fulfils a medical need, for instance, and the price or other economic considerations do not form part of the decision basis in relation to marketing authorisation applications.
>
> In contrast, the indication, use, price etc. of the medicinal product form part of the basis for deciding whether a medicinal product should be granted reimbursement or not. In addition to the primary objective of granting public reimbursement for treatment with medicines, the provisions of the Act in relation to reimbursement consequently also aim at ensuring an expedient use of health security funds and promote the rational use of medicinal products. The fact that a medicinal product is not subject to reimbursement should therefore not be interpreted as an indication that it is less effective, less safe or of a poorer quality than medicinal products subject to reimbursement.”

The price of a medicinal product is thus an integral part of the Danish Medicines Agency’s basis for deciding the reimbursement status.

The Committee’s recommendation to divide the lipid-lowering medicines into two groups has also been questioned: medicinal products subject to general reimbursement without restriction and medicinal products subject to restricted reimbursement, including the fact that the medicinal products within the individual groups are not comparable in every sense.

When the Danish Medicines Agency grants general reimbursement without restriction for some medicinal products and restricted reimbursement for others, this does not imply that the Danish Medicines Agency generally assesses that medicinal products with the same reimbursement status are comparable on all counts.

The Danish Medicines Agency assesses that the lipid-lowering medicinal products comprised all fulfil the basic criterion that the therapeutic value of the medicinal product is reasonable compared to the price. However, for the medicinal products for which restricted reimbursement is granted, the

Danish Medicines Agency is of the opinion that the criterion has solely been fulfilled in the cases stated in the restriction.

Internally within the group of medicinal products for which general reimbursement without restriction is granted, as well as internally within the group with restricted reimbursement, there will be differences in effect, adverse reactions, the volume of documentation available, compliance in the use of the products etc. These issues are not specific to lipid-lowering medicines. What is decisive, however, is whether we assess in each specific case that the medicinal product is overall eligible for reimbursement as stated in the decision.

Finally, concerns have been raised about the fact that the proposed reimbursement status limits the doctors' possibilities of choosing the most appropriate treatment.

In this context, it is noted that the Danish Medicines Agency shares the opinion of the Reimbursement Committee that it will always be rational, as a starting point, to initiate treatment with the cheaper statins eligible for general reimbursement and then supplement or convert the treatment regimen if necessary, e.g. if the treatment objective has not been reached or the treatment is not tolerated.

The Danish Medicines Agency has noted that the Danish College of General Practitioners, in their consultation response of 8 October 2006, expressed their satisfaction with the changes recommended by the Committee, as the College believes the changes to be evidence-based to the greatest degree possible and to entail a considerable simplification of the reimbursement rules.

Information

Doctors and pharmacies will receive information about the new reimbursement status of lipid-lowering medicines in articles in medical journals etc. Other stakeholders will receive a short notice referring to the website of the Danish Medicines Agency where the decision and a brief overview of the current and future reimbursement status will be published.

Conclusion

The division into general reimbursement and restricted reimbursement requires the doctor – as always – to consider his or her prescription, including the justification for prescribing lipid-lowering medicines subject to restricted reimbursement and the choice between these medicines.

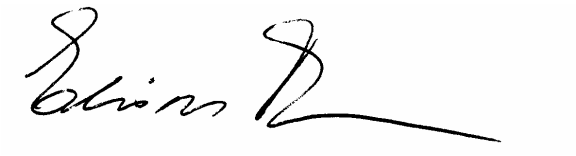
In principle, it will no longer be necessary to apply for single reimbursement for the currently authorised lipid-lowering medicines.

However, it may still be an option in very special cases, e.g. for cholestyramine intended for other uses than normal lipid-lowering therapy.

Complaints guidance

This decision may be brought before the Ministry of the Interior and Health, Slotholmsgade 10-12, DK-1216 Copenhagen. This authority will not, however, be able to assess the scientific evaluation made by the Danish Medicines Agency.

Yours sincerely



Elisabeth Thomsen

Appendix:
A list of your products covered by the decision.