Danish Medicines Agency
Case no. 5315-9
16 January 2009

Appendix I – Note on consultation on proposal for future reimbursement status of medicinal products for cardiovascular diseases in ATC groups C02, C03, C07, C08 and C09

Introduction

Four consultations have been conducted in relation to the reassessment of the reimbursement status of medicinal products for cardiovascular diseases in ATC groups C02, C03, C07, C08 and C09.

The Reimbursement Committee submitted its first recommendation on 29 January 2008. The recommendation was submitted for consultation with a deadline of 5 May 2008.

On the basis of the consultation responses received, the Reimbursement Committee submitted an additional recommendation on 2 September 2008. The additional recommendation contains the comments of the Reimbursement Committee on a number of the medical and pharmaceutical views presented in the consultation responses as well as the Reimbursement Committee's proposal to revised conditions for the general reimbursement for the angiotensin II antagonists. Finally, the Committee also comments on views raised in relation to the undertreatment of hypertension in Denmark combined with financial circumstances.

The additional recommendation underwent consultation with a deadline of 19 September 2008.

In addition, the Danish Medicines Agency has conducted a consultation on intended changes in the reimbursement status of medicinal products in ATC group C08CA (dihydropyridine calcium channel blockers) with a consultation deadline of 11 November 2008 and a consultation on intended changes in the reimbursement status for five combination products in ATC groups C07, C08 and C09. The deadline for consultation responses in relation to this consultation was 11 December 2008.

This note makes reference to the most important points stated in the consultation responses received and contains the comments of the Danish Medicines Agency thereon. However, in relation to the medical and pharmaceutical comments, reference is made, to a large extent, to the additional recommendation of the Reimbursement Committee of 2 September 2008.

Parties to the consultation

Concerned companies:

1A Farma A/S, 2care4 ApS, A/S GEA Farmaceutisk Fabrik, Abacus Medicine ApS, Abbott Scandinavia AB, Actavis A/S, Actavis Group, Actavis Group hf., Actavis Group PTC ehf., Actavis Nordic A/S, Alpharma ApS, Alpharma AS, Alternova A/S, A-Pharma ApS, Arrow Generics Limited, AstraZeneca A/S, AWD Pharma GmbH & CO KG, Baxter A/S, Bayer AG-Leverkusen, Bayer HealthCare, Bayer HealthCare AG, BMM Pharma AB, Boehringer Ingelheim Int. GmbH, Boehringer Ingelheim Pharma GmbH, Bristol-Myers Squibb AB, Bristol-Myers Squibb Pharma EEIG, Copyfarm A/S, Daiichi Sankyo Europe GmbH, Egis Pharmaceuticals UK Ltd, Encysive (UK) Limited, EuroPharmaDK ApS, Ferrosan A/S, Generics (UK) Límited, GlaxoSmithKline Pharma A/S, Hexal A/S, Hexal AG, KRKA Sverige AB,

LEO Pharma A/S, Les Laboratoires Servier, Meda AS, Menarini International Operation, Merck KGaA,Merck NM AB, Merck Sharp & Dohme BV, Mylan AB, Norpharma A/S, Novartis Europharm Ltd., Novartis Healthcare A/S, Nycomed Danmark ApS, OBA - Pharma ApS, Orifarm A/S, Orion Corporation Orion Pharma, Paranova Danmark A/S, Pfizer ApS, PharmaCoDane ApS, Ranbaxy (UK) Limited, ratiopharm GmbH, Roche A/S, Sandoz A/S, Sandoz GmbH, Sanofi Pharma Bristol-Meyers, Sanofi-aventis Denmark A/S, Servier Danmark A/S, Singad Pharma ApS, Solvay Pharmaceutical GmbH, Solvay Pharmaceuticals B.V, Stada Arzneimittel AG, Swedish Orphan A/S, Teva Denmark A/S.

Scientific societies:

Danish Society of Cardiology, Danish Endocrine Society, Danish Hypertension Society, Danish Society for Vascular Surgery, Danish Surgical Society, Danish Medical Society, Danish Society of Nephrology, Danish Paediatric Society, Danish College of General Practitioners, Danish Stroke Society, Danish Society of Geriatrics, Danish Society of Internal Medicine, Danish Society of Clinical Pharmacology and the Danish Society of Obstetrics and Gynaecology.

Patient organisations:

Danish Patients, Disabled Peoples' Organisations Denmark, Danish Heart Foundation, Danish Diabetes Association and the Danish Stroke Association.

In addition, the National Board of Health and the Institute for Rational Pharmacotherapy have been briefed.

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The Reimbursement Committee's 1st recommendation of 29 January 2008 – consultation deadline 5 May 2008

The Danish Medicines Agency received seven consultation responses from concerned companies, nine contributions from scientific societies, four from patient organisations and four from other stakeholders. The responses have been published at the Danish Medicines Agency's website, www.dkma.dk > Companies > General reimbursement > Reassessment of reimbursement status for medicinal products, announcement of 7 July 2008.

We presented all the responses to the Reimbursement Committee, requesting the Committee's comments on the medical and pharmaceutical issues. The responses were discussed at the Committee's meetings on 20 May 2008, 17 June 2008 and 26 August 2008.

The Committee commented on the following medical and pharmaceutical issues in its additional recommendation of 2 September 2008:

- Class effect within the group of ACE inhibitors and the group of angiotensin II antagonists, respectively
- Choice of ACE inhibitors vs. choice of angiotensin II antagonists
- Objections to change of product
- Undertreatment in relation to the reimbursement changes proposed

The Committee also proposed a change in the condition for being granted reimbursement for the angiotensin II antagonists, which the Committee had recommended in its first recommendation, and finally commented on some of the objections in relation to the financial consequences of the change in reimbursement.

1. Medical and pharmaceutical comments

In relation to the medical and pharmaceutical comments raised in the consultation responses, we support the views put forward by the Reimbursement Committee in its first recommendation of 29 January 2008[1] and in its additional recommendation of 2 September 2008[2]. In relation to change of product, compliance and undertreatment, the following comments are added:

1.1 Change of product

Several parties to the consultation have proposed that any changes in the reimbursement status of the cardiovascular products should only apply in future – i.e. for new patients for whom treatment is initiated after a given date – but that the 'old reimbursement status' of the medicinal product should be maintained for patients already undergoing treatment.

Section 152(1) of the Danish Health Act states that the Danish Medicines Agency may decide that the granting of general reimbursement status be conditional upon the medicinal product being prescribed with a view to treatment of specific diseases. Conversely, the Danish Medicines Agency cannot decide that general reimbursement, including general conditional reimbursement, should only apply to a group of patients for whom treatment is initiated with these medicinal products after a fixed deadline.

A consultation response indicated that Sweden has implemented a similar process and similar conditions for the reimbursement for the angiotensin II antagonists, but that this decision only applied to future patients and therefore only applies to new patients as of 1 September 2008.

In Sweden, changes were introduced in the reimbursement status for medicinal product for the treatment of cardiovascular diseases on 1 September 2008, largely corresponding to the future changes in Denmark. In Sweden, general reimbursement for medicinal products in ATC group C07 (beta blockers) was made conditional, however so that the conditions would only apply to new patients. In Denmark, no changes will be made in the reimbursement status of the beta blockers. The other changes introduced in Sweden, including similar conditions for the reimbursement for the angiotensin II antagonists, applied to all patients and thus resulted in a change of product for many of the patients.

In relation to the VALUE study, to which the Reimbursement Committee makes reference in its additional recommendation of 2 September 2008, it should be noted that the authors conclude that the treatment target in case of change of product must be reached "within a relatively short time (weeks rather than months)…..". This is normal and good practice. However, this practice was not observed in the VALUE study, where the change took 3-6 months.

The Danish Medicines Agency, as does the Reimbursement Committee, presupposes that general practitioners perform changes of product gradually, under close monitoring and with respect for the patient's overall pathological picture and treatment. The Agency holds the view that routine checks within a short time after a change of product, including blood pressure checks and any required blood samples, will not result in a deterioration of the patient's treatment and will also detect any differences in response for which corrections can be made.

We make reference to the IRF guidelines for change of product in connection with the treatment of uncomplicated hypertension, from treatment with an angiotensin II antagonist to treatment with an ACE inhibitor or from one ACE inhibitor to another, respectively

[1] http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=13094

[2] http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=14026

(http://www.irf.dk/dk/publikationer/vejledninger/skift_fra_angiotensin-2_antagonist_til_ace-haemmere_ved_ukompliceret_hypertension.htm (in Danish)), which indicates equieffective doses. Furthermore, several regions include guidelines for the general practitioners in their basic list, cf. www.basislisten.dk (in Danish). General practitioners from the individual regions are responsible for the design and the recommendations.

People who are well treated on angiotensin II antagonists can switch to treatment with ACE inhibitors without compromising the effect of the therapy. In case of such a switch, treatment will become cheaper. Specialists in hypertension treatment assume that only up to half of the people treated for hypertension reach the target for optimum treatment. Increased focus on treatment might therefore result in generally better treatment.

1.2 Compliance

Several parties to the consultation state that the Reimbursement Committee should explicitly account for the expected compliance problems in case of a general recommendation of change of treatment, and they make reference to the fact that between 5 and 20 per cent of the patients experience adverse reactions in the form of irritated cough when using ACE inhibitors.

The adverse reactions could be one of the reasons for poor compliance, but it is also well known that financial issues are significant to the compliance of patients. Box 23 of the European guidelines[3] mentions a number of possible causes for lack of compliance.

In its additional recommendation of 2 September 2008, the Committee states that it holds the view that the increased focus on these patients and the lower expenses for medicine resulting from any change in medication will assist in ensuring a greater extent of adequate treatment. Cf. the above, the Danish Medicines Agency supports this assessment and notes that in those cases where patients have irritated cough caused by the ACE inhibitor treatment, the patients should resume treatment with angiotensin II antagonists.

Compliance is a precondition for optimum treatment effect for any medical treatment and is therefore an issue in relation to reimbursement decisions.

1.3 Undertreatment

A number of parties to the consultation state that the authorities (preferably the Danish Medicines Agency and the National Board of Health jointly) should ensure that more patients undergo hypertension treatment, that those patients who are in treatment receive adequate treatment, and that the recommendation is counter-productive in relation to the task of eliminating undertreatment.

The Reimbursement Committee commented on this aspect in its additional recommendation of 2 September 2008. We support the views of the Committee and note that the Danish Medicines Agency administers the rules on reimbursement in the Danish Health Act, and in the administration of these rules, the Agency must ensure appropriate allocation of the funds of the regions and encourage rational use of medical products.

2. Other comments

[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 (www.jhypertension.com)

2.1 Financial aspects

Several parties to the consultations request a health economic analysis of the proposed changes and request that the Reimbursement Committee account for the expected additional costs for the public sector and patients as well as for the expected resource demand for doctors in case of a general recommendation of change of treatment.

We make reference to the Reimbursement Committee's additional recommendation of 2 September 2008, in which it is stated that the Committee is of the opinion that a change of product could take place naturally in connection with these patients' regular control visits to their doctor, but the Committee recognises that a switch would necessitate extra visit(s) to the doctor for the individual patient. The Reimbursement Committee adds that, considering that the medicinal product which the patient is expected to change 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 change would be regained quickly.

In the administration of the reimbursement rules in the Danish Health Act – also in connection with reassessment – the Danish Medicines Agency must assess whether the relationship between the price of a medicinal product and its therapeutic value is reasonable. The assessment of the therapeutic value of a medicinal product takes place according to an established procedure and in accordance with the Danish Medicines Agency's guidelines of 19 May 2008 on applications for general reimbursement for medicinal products (http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=6450), the Danish Medicines Agency's guidelines of 8 June 2005 on the procedure for reassessment of the reimbursement status of medicinal products http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=6306 and the Danish Medicines Agency's guidelines of 4 July 2006 for evaluation and comparison of medicinal products in reassessments of reimbursement status http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=10107 by comparing the medicinal product in question with relevant treatment alternatives for the same disease. It has not been assumed that the Danish Medicines Agency would make a health economic analysis of the consequences of changes in reimbursement resulting from a reassessment of the reimbursement status of medicinal products. The financial consequences of a change of product as a result of a reimbursement change is not a criterion which forms part of the assessment of the therapeutic value of a medicinal product, and as such, it does not form part of the basis for decision.

The Danish Medicines Agency emphasises the Reimbursement Committee's reference to the fact that the medicinal products in ATC group C09 are recommended equally for all indications and that there is class effect within each of the medicinal product groups ACE inhibitors and angiotensin II antagonists, and on this basis, the Agency estimates that the therapeutic value of these medicinal products is equal.

In relation to prices, the decision for medicinal products in ATC group C09 states that the average lowest price of treatment per day for oral treatment with the ACE inhibitors (individual substances) which will maintain their general reimbursement – captopril, enalapril, lisinopril, ramipril and trandolapril – is between DKK 0.36 and DKK 1.37. By comparison, the average lowest price of treatment per day for oral treatment with the ACE inhibitors (individual substances) which will lose their general reimbursement – perindopril, quinapril, benazepril and fosinopril – is between DKK 3.80 and DKK 22.76.

For the angiotensin II antagonists for which the reimbursement status is changed to general conditional reimbursement, the average lowest price of treatment per day for oral treatment with the individual substances losartan, eprosartan, valsartan, irbesartan, candesartan, telmisartan, olmesartan and aliskiren is between DKK 5.29 and DKK 11.22.

Reports to the Danish Medicines Agency's medicinal product statistics show that the average annual expenses per patient for treatment with ACE inhibitors which will maintain their general reimbursement was DKK 431 for the period 1 July 2007 to 30 June 2008. The average annual expenses for treatment of a patient with the ACE inhibitors which will lose their general reimbursement, was DKK 2,000 for the same period, and the average annual expenses per patient for treatment with angiotensin II antagonists which will be granted general conditional reimbursement, was DKK 2,804 for the same period. The current price level is comparable to the price level applying for this period.

The Danish Medicines Agency estimates that a change of product can be done during a routine consultation, whereas a check of blood pressure requires one – possibly two – additional consultations. If the change is from an angiotensin II antagonist to an ACE inhibitor, the kidney function must also be checked via a blood sample.

The expenses for a doctor's consultation amount to DKK 125.61[4]. The expenses for blood sampling with a view to checking kidney function as well as blood sample analysis amounts to DKK 95.97.[5]

Based on the price level for these medicinal products applicable at the time of this decision, and given the fact that the treatment is often lifelong, the Danish Medicines Agency is also of the opinion that the additional expenses incurred in switching the individual patient will by far be outweighed by the smaller expenses for the medicinal product.

Several parties to the consultation have stated that the angiotensin II antagonist Cozaar is coming off patent. With reference to the Agency's established procedure of price comparisons in connection with reimbursement decisions described in the guidelines mentioned above, any future price decreases, e.g. due to patent expiries, do not form part of the reimbursement decisions of the Danish Medicines Agency.

A number of consultation responses indicate that the Reimbursement Committee supposedly stated a savings potential in relation to the change of reimbursement status proposed by the Committee.

The Reimbursement Committee has not stated any savings potential in connection with its recommendation. In its additional recommendation of 2 September 2008, the Committee states that it is of the opinion that the medicinal products with the suggested changes to the current reimbursement status will be granted the reimbursement status to which their efficacy – and other aspects – entitles them, assessed from the perspective of rational pharmacotherapy.

At a meeting held on 31 January 2008, hosted by the Institute for Rational Pharmacotherapy, the Danish Medicines Agency presented theoretical estimated maximum annual savings for patients and the public sector, as a consequence of the proposal for the change of reimbursement, exclusively for medicinal product expenses, of between DKK 245 and 275 million. The estimates were based on the prices of the medicinal products involved and the number of patients undergoing treatment with these. A large number of important reservations were made in relation to this estimate.

[4] Agreement for general practitioners (Overenskomst om Almen lægegerning), applicable from 1 October 2008. Figures for coverage group 1.

[5] Agreement for general practitioners (Overenskomst om Almen lægegerning), applicable from 1 October 2008. Figures for coverage group 1 and prices from Laboratory of Copenhagen General Practitioners, 15 December 2008.

Finally, it should be noted that the purpose of initiating a regular reassessment of the reimbursement status of medicinal products is to assess whether the preconditions of the original decision to grant or deny reimbursement are still valid and thus still able to support rational application of the region's funds. The purpose of the reassessment of the reimbursement status of medicinal product is not to implement savings.

2.2 Price comparisons

As mentioned above, several parties to the consultations indicate that a patent on Cozaar (losartan) expires during 2009 (September is mentioned) and that as a consequence, a significantly lower price of losartan should be expected and that a new reassessment should be expected subsequently due to the financial circumstances.

In decisions on general reimbursement, including general conditional reimbursement, we must assess whether the relationship between the price of a medicinal product and its therapeutic value is reasonable, cf. Danish executive order no. 180 of 17 March 2005 on reimbursement. When assessing these circumstances, we must look at the price of the medicinal product at the time of making the decision. The detailed procedure for the price calculation and comparison in relation to reassessment is described in the applicable guidelines of 4 July 2006 on evaluation and comparison of medicinal products in reassessments of reimbursement status
http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=10107

This states, among other things, that the comparison is based on the lowest price per unit among all products and pack sizes of the medicinal product in question, i.e. the lowest reimbursement price for all packs marketed (the lowest unit reimbursement price) and on an average of these unit prices for the latest three months, corresponding to six price periods. We adhere to these guidelines in relation to price comparison in connection with the reassessment process. We do not include information on expected future price decreases, e.g. as a consequence of patent expiries. Before generic medicinal products are marketed in Denmark, and a price is notified to the Danish Medicines Agency in this connection, these will thus not be included in our assessments in relation to the reimbursement status of a medicinal product.

It is correct that if the Danish Medicines Agency is made aware that significant changes have occurred in the preconditions for a decision to grant or recall general reimbursement, including general conditional reimbursement, this decision is reassessed according to the general rules. Furthermore, a pharmaceutical company has the opportunity to apply for general reimbursement for a medicinal product at any time.

The Danish Medicines Agency's use of prices in connection with the reassessment process is criticised by a party to the consultation, and it is stated that only in very rare cases are simple price comparisons sufficient to make a well-founded decision on reimbursement status. It is added that since medicinal products, as regards effects and adverse reactions etc. are completely similar in only very special cases, very simple price comparisons are – as a general rule – pointless.

The Danish Medicines Agency's use of price comparisons in the reassessment process takes place according to the guidelines mentioned above which, inter alia, state that the assessment of the therapeutic value of a medicinal product must be based on a comparison of the medicinal product with other relevant treatment of the same disease.

The assessment of the therapeutic value of a medicinal product includes, according to an established procedure and in accordance with the Danish Medicines Agency's guidelines of 19 May 2008 on

applications for general reimbursement for medicinal products (http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=6450), the Danish Medicines Agency's guidelines of 8 June 2005 on the procedure for reassessment of the reimbursement status of medicinal products (http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=6306) and the Danish Medicines Agency's guidelines of 4 July 2006 for evaluation and comparison of medicinal products in reassessments of reimbursement status (http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=10109), a medical assessment of which treatment alternatives are a relevant basis of comparison for the medicinal product, and in those cases where other medicinal products exist which can be said to be a relevant treatment alternative, a comparison is made of the price of one medical treatment vs. the other.

Finally, one party to the consultation encourages the authorities to reassess the previous practice for use of information regarding price/economy in decisions on reimbursement. We would like to make reference to the fact that in an agreement between the Ministry of Health and Prevention and the Danish Association of the Pharmaceutical Industry on a ceiling on medicinal product prices for the period 2009-2011, the parties agreed that during the agreement period, they will discuss the use of medical product prices in connection with decisions on the rational use of medicinal products in the Danish health service.

The Danish Medicines Agency is also encouraged to indicate which price ceiling the Agency has used for the individual medicinal product classes. Information is also requested on the level of the ceiling for the maximum number of patients that can be treated with a specific medicinal product before the reimbursement status is changed.

There is free price formation on medicinal products in Denmark, and the Danish Medicines Agency does not apply price ceilings in its reimbursement decisions. One of the main criteria for granting general reimbursement is whether the relationship between the price of a medicinal product and its therapeutic value is reasonable, cf. above.

If a medicinal product is more expensive than relevant treatment alternatives, it is assessed whether any differences in effect and adverse reactions etc. justify the additional cost. If this criterion is seen to be met, the medicinal product can obtain or maintain general reimbursement.

If the criterion is only seen to be met when the medicinal product is used for the treatment of a specific disease, but not for all indications of the medicinal product, the medicinal product will, as a starting point, obtain or maintain general conditional reimbursement targeted at the treatment of the specific disease. However, if the assessment is that the medicinal product has found its place in the treatment of that disease, and there is not estimated to be any risk of the medicinal product being used as a first-line treatment in cases where this should not occur, the medicinal product will, according to the established procedure, obtain or maintain general unconditional reimbursement.

The starting point is therefore that if an additional cost cannot be justified from a medical view, cf. above, the medicinal product is not entitled to general reimbursement, including general conditional reimbursement, regardless of how few patients are undergoing treatment with the medicinal product in question.

The Danish Medicines Agency monitors the consumption and prices of all medicinal products receiving general reimbursement.

As mentioned above, there is free pricing on medicinal products in Denmark, and the price of a medicinal product can be changed every two weeks. The reassessment of the reimbursement status of medicinal products must be seen in this light. This is also noted by the Reimbursement Committee in its first recommendation of 29 January 2008.

2.3 Procedure

Other comments on the consultation responses indicate that the Reimbursement Committee should conduct and document an individual assessment on a product-by-product basis and that the recommendation of the Reimbursement Committee is, to a considerable extent, based on an assessment of class effects between the different products without taking the unique properties of the products into consideration.

We refer to what the Reimbursement Committee mentioned in its additional recommendation of 2 September 2008 under the heading 'Class effect within the group of ACE inhibitors and the group of angiotensin II antagonists, respectively'. Here, the Committee states that it is of the opinion 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 method was also described in the Danish Medicines Agency's guidelines of 4 July 2006 for evaluation and comparison of medicinal products in reassessments of reimbursement status (http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=10109), where it is stated that the primary aspect in an assessment of two or more medicinal products against each other is a comparison of effect and adverse reactions in connection with relevant diseases and the clinical significance of any differences.

We also refer to the Committee's comments on the individual active substances and pharmaceutical forms, as appears from Appendix B to the Committee's first recommendation of 29 January 2008 (http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=13094).

The Reimbursement Committee's information gathering and documentation of the use of other sources of information than the approved indications of the medicinal products are criticised.

In its first recommendation, the Reimbursement Committee submitted a list of literature containing references to national and international guidelines, recommendations, background notes etc. which the Committee emphasises in its recommendation. The additional recommendation also makes reference to one additional pharmaceutical reference.

Several parties to the consultation criticise the fact that comparisons between medicinal products in the reassessment process are not based on the approved indications of the medicinal products, which require comprehensive and expensive documentation. The clinical guidelines etc. to which the Committee makes reference in its recommendations, are evidence-based.

The comments on the act to amend the Danish Health Service Act and the Social Service Act, published as Act no. 1045 of 23 December 1998, today replaced by the Danish Health Act[6] (http://lms-lw.lovportaler.dk/ShowDoc.aspx?docId=lov20050546#p143 (in Danish)), state the following:

"In connection with the authorisation of a medicinal product, requirements cannot be made that a medicinal product e.g. fulfils a medical need, and the price or other financial considerations do not form part of the basis for the decision in case of applications for marketing authorisation. Contrary hereto, the

[6] Cf. Danish consolidation act no. 95 of 7 February 2008, as amended.

indication, use, price etc. of a medicinal product do form part of the basis for the decision as to whether or not a medicinal product should be granted reimbursement. In addition to the primary objective of providing public subsidies for medicinal treatment, the provisions of the act on reimbursement thus also have the objective of ensuring an appropriate use of the public health funds and to encourage rational use of medical products. Therefore, the fact that a medicinal product has not been granted a reimbursement, cannot be interpreted to mean that it is less efficient, less safe or of poorer quality than medicinal products with reimbursement."

The Danish Medicines Agency's assessment of the therapeutic value of a medicinal product in relation to the question of reimbursement is based on these considerations.

2.4 EU law

One party to the consultation states:

> "It must be assumed to be incompatible with the principles set out in the Article 28 on the free movement of goods of the treaty if the reimbursement system is constructed in such a way that it favours generic products via subsidy barriers.
>
> In Communication 86/C310/08 on the compatibility of Article 30 (Article 28) with the measures of the member states concerning reimbursements, the Commission states, among other things:
>
> The Commission finds it to be incompatible with the above principle:
> - if, for one or more therapeutic classes, it is determined that proprietary products are not entitled to reimbursement, regardless of their price;
> - if, for each therapeutic class or all therapeutic classes, only a predetermined number of medicinal products are entitled to reimbursement.
>
> The reimbursement decision intended here does not aim to pursue objectives of this character. It does have the de facto effect, however, that generic products are heavily favoured."

Concerning the practice of the European Court of Justice that the provisions of the treaty do not apply to harmonised areas, Article 28 of the treaty cannot have been violated to the extent that the question is controlled by directives.

The question of the inclusion of medicinal products under national health insurance systems is regulated by Council directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems.

Article 6(2) states that "Any decision not to include a medicinal product in the list of medicinal products covered by the health insurance system shall contain a statement of reasons based upon objective and verifiable criteria, including, if appropriate, any expert opinions or recommendations on which the decision is based…"

The criteria for general reimbursement, including general conditional reimbursement, have been determined in Danish executive order no. 180 of 17 March 2005 on reimbursement, as amended. One of the main criteria for general reimbursement, including general conditional reimbursement, is that the relationship between the price of a medicinal product and its therapeutic value must be reasonable. This assessment, according to the established procedure, is based on a comparison of medicinal products with comparable effect and adverse reactions in case of relevant indications and an assessment of the clinical

significance of any difference, cf. also the Danish Medicines Agency's guidelines of 4 July 2006 on evaluation and comparison of medicinal products in reassessments of reimbursement status.

In Communication 86/C310/08, the Commission states: "The medicinal market presents certain characteristics which clearly differ from the markets for other consumables. Firstly, the case is normally that the end consumer of a specific medicinal product has only very limited influence on the choice of medicine – at least in the case of prescribed medicine. In addition, the demand for a medicinal product usually depends on the treatment of a specific disease, and the different forms of medicine are only generic to a small extent. Secondly, the medicinal market is characterised by the fact that, ultimately, the national health insurance system and not the consumer pays the medicinal costs.

Because society is bearing the brunt of the expenses, it is therefore understandable that the member states attempt to limit medicinal expenses. In view of this, most member states have passed legal provisions on the control of medicinal prices and on national health insurance payment of medicinal reimbursements. These measures are within the framework of the health policy of the member states and aim at providing the best possible treatment for the citizens as a whole without incurring unreasonable costs to society.

In principle, such measures are compatible with EU law, provided that their restrictive impacts on the free movement of goods is not disproportionate to the legitimate goal intended. It is especially important that such measures do not entail any type of harmful discrimination to goods imported from other member states and that they do not entail that the sale of imported goods becomes unprofitable, impossible or more difficult than the sale of domestic goods, and nor may they entail that certain import patterns are made impossible or become more costly than others."

The Danish medicinal reimbursement system entails no type of harmful discrimination to goods imported from other member states and does not entail that the sale of imported goods becomes unprofitable, impossible or more difficult than the sale of domestic goods, and nor does it entail that certain import patterns are made impossible or become more costly than others.

The Danish medicinal reimbursement system is not based on a system in which "brand products are not entitled to reimbursement, regardless of their price" or in which "for each therapeutic class or all therapeutic classes, only a predetermined number of medicinal products are entitled to reimbursement."

In the same consultation response, reference is also made to the Commission's response to a written enquiry from Amadeo to the Commission on 30 November 1994, and the following is stated: "In our view, this shows that a general system, be it a price control system or a reimbursement system, may not be organised in such a way that it makes the supply of patented products more difficult by favouring prices which are too low to cover the development costs etc. of patented products. This becomes especially important considering the intention of the recommendation to place Aliskiren under the same condition as the AIIA products, which entails a considerable risk that this new product with a long remaining patent period and which, incidentally, is placed in its own ATC group, is equalled to the AIIA products and displaced due to the favouring of the ACE II products."

The Italian enquiry regards a price fixing system, in which connection the Commission expresses concern that the Italian authorities may fix prices on Italian medicinal products at a lower level than the other member states.

The Italian enquiry thus pertains to medicinal price control. However, the Danish medicinal reimbursement system is not a price fixing system or a price control system, but a medicinal reimbursement system.

Such systems are comprised by the Council's directive 89/105/EEC, cf. above.

2.5 Patent law

One party to the consultations states: "The Reimbursement Committee should include the patent status of the products in the basis for decisions: Authority decisions on reimbursement should respect the patent protection of the products, in that such decisions should not undermine patents and other intellectual property rights. With its simple price comparisons, the Reimbursement Committee systematically equals products with and without patents, and the recommendation thus in reality undermines the intellectual property rights of the companies. This is particularly evident for the ACE inhibitors, as the recommendation entails a reimbursement differentiation between products with and without patents."

It is further stated that it should be regarded as unprofessional and disproportional to compare the price of products which are off patent with patented products.

The Danish Medicines Agency must assess whether the relationship between the therapeutic value and the price of the medicinal product is reasonable, cf. section 1(2), item 2, of Danish executive order no. 180 of 17 March 2005 on reimbursement as amended (http://lms-lw.lovportaler.dk/ShowDoc.aspx?docId=bek20050180-full (in Danish)). The basis for decision on the reimbursement for a medicinal product does not contain any legal base for including the patent status of a medicinal product.

2.6 Practical implementation

Several parties to the consultations point to the fact that the Danish Medicines Agency must pay attention to the practical implementation of future changes.

We refer to what is stated in the decisions on information and to the fact that the decisions will not enter into force until 13 July 2009.

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The Reimbursement Committee's additional recommendation of 2 September 2008 – consultation deadline 19 September 2008

The Danish Medicines Agency received five consultation responses from concerned companies, two contributions from scientific societies, one from a patient organisation and one contribution from another stakeholder. The responses have been published at the Danish Medicines Agency's website, www.dkma.dk > Companies > General reimbursement > Reassessment of reimbursement status for medicinal products, announcement of 21 November 2008.

3. Medical and pharmaceutical comments

All responses have been presented to the Reimbursement Committee, requesting the Committee's comments on the medical issues raised by the parties to the consultations. The responses were discussed at the Committee's meeting on 23 September 2008. The Committee maintained what was indicated in the additional recommendation and found no cause to add anything further to its recommendations.

In relation to the medical and pharmaceutical issues, the Danish Medicines Agency will support the statements made by the Reimbursement Committee. As for specific patient groups and conditions for reimbursement, the following was added:

3.1 Specific patient groups

Some consultation responses express the view that the Reimbursement Committee has exclusively focused on hypertension patients and has not taken other patient groups and the documentation existing for the treatment of these into consideration. From the recommendations of the Committee, it is apparent that the use of the medicinal products for different patient groups, including for the treatment of hypertension patients with other diagnoses such as diabetes, cardiovascular diseases and previous apoplexy or for the treatment of other diseases than hypertension, e.g. heart insufficiency, has been an integrated part of the Committee's assessment of the reimbursement status of the medicinal products.

We support the views of the Committee. We also note that the consultation responses do not question the references to the European guidelines to which the Committee makes reference it its recommendations. It is thus the assessment of the Committee that within the groups of ACE inhibitors and angiotensin II antagonists, respectively, there are no clinically relevant differences in effect and adverse reactions, and that the recommendation of the two substance groups is equal for all indications.

3.2. Conditions

There is a difference in the adverse reactions of ACE inhibitors and angiotensin II antagonists, and therefore, the Committee has recommended and the Danish Medicines Agency decided that there should be conditional reimbursement for angiotensin II antagonists. This ensures that the patients who cannot be treated with less expensive ACE inhibitors eligible for general reimbursement and who thus require treatment with angiotensin II antagonists, can receive this treatment with reimbursement.

With its decisions, the Danish Medicines Agency has observed the recommendation of the Reimbursement Committee in its additional recommendation of 2 September 2008, in which the Committee suggests a revised condition for the angiotensin II antagonists, taking into consideration the exceptional circumstances in which treatment with less expensive medicinal products eligible for general reimbursement which act on the renin-angiotensin system, according to the general practitioner's overall clinical assessment of the patient's condition, is not appropriate.

This extension of the condition provides for a use of angiotensin II antagonists in those exceptional circumstances where the general practitioner, based on an overall clinical assessment of the patient's condition, finds that treatment with angiotensin II antagonists is most appropriate for the patient.

The same considerations underlie the conditions for the reimbursement for some dihydropyridine calcium channel blockers. There is class effect among these, but differences in adverse reactions and drug interactions which, for some patients, will mean that one substance is more appropriate than another. Therefore, the general practitioner will still be able to prescribe these medicinal products with reimbursement when the patient meets the reimbursement condition.

One party to the consultation suggests that the reimbursement for the expensive ACE inhibitors be conditional in line with the reimbursement for the angiotensin II antagonists. The reason why the Danish Medicines Agency does not find that there is basis for making the general reimbursement for the expensive ACE inhibitors conditional is that the class effect within this group is so comprehensive that it is very unlikely that a patient should not be eligible for treatment with one of the less expensive ACE inhibitors. If there is a special reason for continued treatment of a patient with one of the expensive ACE

inhibitors, the general practitioner can apply for single reimbursement in accordance with the general rules in this area.

The choice of medicinal product(s) is always an overall assessment which the general practitioner must base on a number of clinical and medical circumstances supported by financial considerations. The objective of the reimbursement system is to support such rational use of medicinal products.

4. Other comments

4.1 Financial aspects

Several parties to the consultations believe that the financial aspects have not been sufficiently considered.

We refer to the above under item 1.2.

4.2 The principle of equality

One party to the consultations states that it would violate the principle of equality to maintain the reimbursement for an expensive ACE inhibitor combination based on compliance considerations without taking the same considerations in regard to angiotensin II antagonists. With reference to a lack of consistency in the Committee's recommendation in relation to the individual products and the fact that reimbursements are recommended for more expensive medicinal products without any proof of additive effect, one party to the consultation finds that the recommendations of the Reimbursement Committee are in violation of the principle of equality.

We refer to our decisions. We find that the changes made to reimbursement status – including in relation to combinations products in ATC groups C07, C08 and C09 – have been made in consistency with the principle of equality.

4.3 Compliance

One party to the consultation would like the Danish Medicines Agency to include compliance in the basis for decision on the changed reimbursement status.

We refer to the above under item 1.4.

4.4 EU law

One party to the consultations states: "It is clear from the European Court of Justice in case C-238/82 that the important criterion is whether the products have the same therapeutic effect. It is very clear that Coversyl Novum and its combinations are not having the same effect and documentation as the different cheaper ACE inhibitors. "

The judgment of the European Court of Justice of 7 February 1984 in case no. 238/82 'Duphar' concerned, among other things, the question whether limitations of certain medicinal products are compatible with Article 30 of the treaty [now Article 28].

This area is now regulated by Council directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems. In accordance with the practice of the European Court of Justice that the provisions of the treaty do not apply to harmonised areas, Article 28 of the treaty cannot have been violated to the extent that the question is controlled by directives.

The criteria for general reimbursement, including general conditional reimbursement, have been set out in Danish executive order no. 180 of 17 March 2005, as amended. One of the main criteria for general reimbursement, including general conditional reimbursement is that the relationship between the price of the medicinal product and its therapeutic value is reasonable. This assessment, according to established procedure, is based on a comparison of medicinal products with comparable effect and adverse reactions in case of relevant indications and an assessment of the clinical significance of any difference, cf. also the Danish Medicines Agency's guidelines of 4 July 2006 on evaluation and comparison of medicinal products reassessments of reimbursement status.

In the Duphar judgment, the Court states that: "Provisions adopted within the framework of a compulsory national healthcare scheme with the object of refusing insured persons the right to be supplied, at the expense of the insurance institution, with specifically named medicinal preparations are compatible with Article 30 [Article 28] of the treaty if the determination of the excluded medicinal preparations involves no discrimination regarding the origin of the products and is carried out on the basis of objective and verifiable criteria, such as the existence on the market of other, less expensive products having the same therapeutic effect…."

In this judgment, the Court acknowledges that Community law does not detract from the powers of member states to organize their social security systems and to adopt, in particular, provisions intended to govern the consumption of pharmaceutical preparations in order to promote the financial stability of their healthcare insurance schemes. However, the Court notes that in order to be compatible with the treaty, such systems must be based on objective and verifiable criteria without reference to the origin of the products. Today, this is codified in Council directive 89/105/EEC. With the judgment, the Court does not exclude other objective and verifiable criteria than "that there are other, less expensive products in the market with the same therapeutic effect….", and the Danish Medicines Agency thus does not concur that "the important criterion is whether the products have the same therapeutic effect."

What is important is that the decision to exclude a medicinal product from the list of medicinal products covered by the health security system must contain a reason based on objective, verifiable criteria, cf. Article 6(2) of Council directive 89/105/EEC.

4.5 Objective and verifiable criteria

One party to the consultation states that the reasons of the Reimbursement Committee are not based on objective and verifiable criteria because the Commission takes its starting point in its experience from clinical everyday experiences. Another party to the consultations finds that inclusion of subjective experiences from everyday life entails a risk that the development towards a health service which should use optimum evidence-based treatment is unnecessarily delayed.

The Reimbursement Committee's recommendation shows that the 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 evaluation and comparison of medicinal products in reassessments of the reimbursement status for medicinal products.

Both of these publications refer to the relevant regulatory framework for the reassessment process, which is also evident from the Danish Medicines Agency's decisions, including in particular the criterion that the relationship between the therapeutic value and the price of a medicinal product is reasonable.

In its first recommendation, the Committee states that its assessment of the different active substances is based on the Committee's clinical experience and that it relies on the recommendations given in clinical guidelines etc., cf. the list of literature. Danish as well as international clinical guidelines are – as one party to the consultations also indicates – based on evidence-based treatments.

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The Danish Medicines Agency's consultation on reassessment of the reimbursement status for dihydropyridine calcium channel blockers (ATC group C08CA) – consultation deadline 11 November 2008

The Danish Medicines Agency received four consultation responses from concerned companies, one contribution from a scientific society and one contribution from another stakeholder. The responses have been published at the Danish Medicines Agency's website, www.dkma.dk > Companies > General reimbursement > Reassessment of reimbursement status for medicinal products, announcement of 19 December 2008.

5. Medical and pharmaceutical comments

5.1 Change of product

Objections are raised against changes of product, including the risk of lacking blood-pressure control and consequent complications as well as the risk of adverse reactions, and general regrets are raised concerning change of product for well-treated patients.

We refer to the above under item 1.1. on change of product, which also applies in relation to the dihydropyridine calcium channel blockers.

5.2 Consumption

With respect to an occurrence of ankle oedema of at least 20 per cent in connection with treatment using amlodipine, one consultation response indicated that it is not understandable that a consumption of lercanidipine of 4.9 % out of the overall consumption of dihydropyridine calcium channel blockers is not rational.

In relation to lacidipine, it is indicated that lacidipine has a documented lower risk of causing oedemas compared to amlodipine, and with reference to the fact that less than 1% of the overall consumption of dihydropyridine calcium channel blockers takes place in treatment with lacidipine, it is stated that there are no indications that lacidipine is used inappropriately.

We refer to what was stated in our decision concerning ATC group C08.

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The Danish Medicines Agency's consultation on reassessment of the reimbursement status for combination products in ATC groups C07, C08 and C09 – consultation deadline 11 December 2008

The Danish Medicines Agency received four consultation responses from concerned companies. The responses have been published at the Danish Medicines Agency's website, www.dkma.dk > Companies

> General reimbursement > Reassessment of reimbursement status for medicinal products, announcement of 2 February 2009.

6. Medical and pharmaceutical comments

6.1 Combination products

Some consultation responses state that combination products have a place in the treatment in relation to compliance.

The Danish Medicines Agency agrees that combination products may support good compliance in the use of medicinal products. However, the Danish Medicines Agency does not find in general that compliance alone can justify a price which significantly exceeds the sum of the prices for the individual substances (or where relevant: the prices of less expensive comparable analogue individual substances in equieffective doses).

It applies to some of the combination products for which the reimbursement status will be changed that the patient can be treated with another similar combination product with general reimbursement. For some, the changes mean that the patient now has to undergo treatment with individual substances, i.e. take two tablets instead of one, and for very few, the changes mean that the patient must take several tablets to achieve a similar dose. However, common to all these cases is the fact that the expenses for the medicinal treatment will be significantly reduced. In those exceptional circumstances where the general practitioner, based on a clinical assessment of the patient's condition, believes treatment with combination products to be necessary, the general practitioner may apply for single reimbursement under the general rules.

7. Other comments

7.1 Coversical

The combination product Coversical was granted general reimbursement on 19 September 2008. An explanation is requested as to why the Reimbursement Committee and the Danish Medicines Agency, in September 2008 assessed the relationship between the therapeutic value and the price to be reasonable, and why this assessment has subsequently changed.

The Committee's recommendation of 5 September 2008 and the decision of the Danish Medicines Agency are based on the principle of equality. As is evident from the Committee's recommendation, the Committee found "that the relationship between the price and the therapeutic value is reasonable when the treatment with Coversical is compared with treatment with perindopril and amlodipine in separate formulations, as medicinal products containing either perindopril or amlodipine are currently eligible for general reimbursement."

With the current decisions, perindopril will lose the general reimbursement, cf. the reasons in the decision for ATC group C09. Furthermore, we refer to the reason for Coversical losing general reimbursement in that same decision.

In those exceptional circumstances where the general practitioner assesses that treatment with a combination product is necessary out of consideration for the patient's compliance, and no such product is available with general reimbursement, an application can be made for single reimbursement.

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