LÆGEMIDDEL STYRELSEN
DANISH MEDICINES AGENCY

For companies which, as of 31 May 2010 or before,
have marketed one or more medicinal products in ATC groups C09C, C09D and C09X containing eprosartan, valsartan, irbesartan, candesartan, telmisartan, olmesartan or aliskiren

Decision on the future reimbursement status of medicinal products in ATC groups C09C, C09D and C09X

11 June 2010

Case no.:
5315-2

With this decision, the Danish Medicines Agency concludes the ad hoc reassessment of the reimbursement status of all medicinal products in ATC groups C09C, C09D and C09X containing eprosartan, valsartan, irbesartan, candesartan, telmisartan, olmesartan or aliskiren which are approved for marketing in Denmark and for which a price is or has been notified to the Agency as at 31 May 2010.

This ad hoc reassessment is caused by a significant reduction in the reimbursement price of medicinal products containing losartan due to the introduction of generics.

The decision will become effective **as of 15 November 2010**.

Presentation
On 29 March 2010, the Reimbursement Committee presented its recommendation on the future reimbursement status of the medicinal products to the Danish Medicines Agency. We refer to the information in the recommendation as regards the course of the case. The Committee's recommendation with appendices is available at http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=16296.

The Committee's recommendation has been submitted to the concerned companies and relevant scientific societies for consultation. Twelve consultation responses were received, which are available (in Danish) at http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=17332.

All consultation responses were presented to the Committee at a meeting held on 18 May 2010. The Committee maintained its recommendation of 29 March 2010.

Please see the consultation memorandum enclosed as Appendix 1 for the most important viewpoints stated in the consultation responses in relation to the decision and the Agency's comments thereon.

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The prices on which the Committee's recommendation was based appear from Appendix B to the Committee's recommendation. In support of this decision, the Agency has prepared a new price survey (Appendix 2) based on six price periods, the first period beginning on 8 March 2010 and the last period beginning on 17 May 2010. Prices of treatment and unit prices have been calculated in accordance with the Agency's guidelines of 8 June 2005 on the procedure for the reassessment of the reimbursement status of medicinal products and the Agency's guidelines of 4 July 2006 for the assessment and comparison of medicinal products in connection with the reassessment of the reimbursement status of medicinal products. As for the combination products, the actual marketed strengths are used as the basis.

Please find below the decision and the grounds on which it was made, the regulatory framework and the complaint instructions.

Decision

1.
The reimbursement status of individual substances in ATC groups C09C (angiotensin II antagonists) and C09X (renin inhibitors) containing:

- eprosartan (C09CA02)
- valsartan (C09CA03)
- irbesartan (C09CA04)
- candesartan (C09CA06)
- telmisartan (C09CA07)
- olmesartan (C09CA08)
- aliskiren (C09XA02)

will be changed from general conditional reimbursement to no general reimbursement.

In the opinion of the Danish Medicines Agency, these medicinal products *do not meet* the criteria for general reimbursement, cf. section 1(2), item 2, of the Danish executive order on reimbursement.

With reference to section 144(2) of the Danish Health Act, the Agency is of the opinion that it is not possible to identify specific diseases or groups of people for which treatment with these medicinal products meets the criteria set out in the executive order on reimbursement for being granted general reimbursement (general conditional reimbursement), cf. section 1(2) of the executive order.

In relation to aliskiren, the Agency assesses that general conditional reimbursement for aliskiren granted to those few patients where treatment with

medicinal products eligible for general reimbursement acting on the renin-angiotensin system (medicinal products containing ACE inhibitors: enalapril, lisinopril, ramipril or trandolapril and the angiotensin II antagonist losartan) has been considered to be inadequate entails the risk that the medicinal product will be used as first-line treatment, even though this should not be the case in the opinion of the Agency, cf. section 1(3), item 5, of the executive order on reimbursement.

2.
The reimbursement status of combination products in ATC groups C09D (angiotensin II antagonists) and C09X (renin inhibitors) containing:

- eprosartan and hydrochlorothiazide (C09DA02)
- valsartan and hydrochlorothiazide (C09DA03)
- irbesartan and hydrochlorothiazide (C09DA04)
- candesartan and hydrochlorothiazide (C09DA06)
- telmisartan and hydrochlorothiazide (C09DA07)
- olmesartan and hydrochlorothiazide (C09DA08)
- valsartan and amlodipine (C09DB01)
- valsartan, amlodipine and hydrochlorothiazide (C09DX01)
- aliskiren and hydrochlorothiazide (C09XA52)

will be changed from general conditional reimbursement to no general reimbursement.

In the opinion of the Agency, these medicinal products *do not meet* the criteria for general reimbursement, cf. section 1(2), item 2, of the Danish executive order on reimbursement.[1]

With reference to section 144(2) of the Danish Health Act, the Agency is of the opinion that it is not possible to identify specific diseases or groups of people for which treatment with these medicinal products meets the criteria set out in the executive order on reimbursement for being granted general reimbursement (general conditional reimbursement), cf. section 1(2) of the executive order.

In relation to aliskiren and hydrochlorotiazide, the Agency assesses that general conditional reimbursement for aliskiren and hydrochlorotiazide granted to those few patients where treatment with medicinal products eligible for general reimbursement acting on the renin-angiotensin system (medicinal products containing ACE inhibitors: enalapril, lisinopril, ramipril or trandolapril and the angiotensin II antagonist losartan) has been considered to be inadequate entails the risk that the medicinal product will be used as first-line treatment, even though this should not be the case in the

[1]Danish executive order no. 180 of 17 March 2005

opinion of the Agency, cf. section 1(3), item 5, of the executive order on reimbursement.

Grounds

Re 1. – Individual substances containing angiotensin II antagonists
Appendix 2 shows that the average lowest price of treatment per day for treatment with medicinal products containing the individual substance losartan is between DKK 0.62 and DKK 0.75.

In comparison, the average lowest price of treatment per day for treatment with medicinal products containing the individual substances eprosartan, valsartan, irbesartan, candesartan, telmisartan and olmesartan is between DKK 5.29 and DKK 10.92.

We emphasise the fact that the Reimbursement Committee in its recommendation of 29 March 2010 states that there is a class effect among all angiotensin II antagonists and that the medicinal products are recommended equally for all indications.

Against this background, the Danish Medicines Agency finds that the relationship between the price of medicinal products containing the individual substances eprosartan, valsartan, irbesartan, candesartan, telmisartan and olmesartan and their therapeutic value is not reasonable compared to medicinal products containing the individual substance losartan.

With reference to section 144(2) of the Danish Health Act, the Agency is of the opinion that it is not possible to identify specific diseases or groups of people for which treatment with these medicinal products meets the criteria set out in the executive order on reimbursement for being granted general reimbursement (general conditional reimbursement), cf. section 1(2) of the executive order.

Re 2. – Combination products – angiotensin II antagonists and hydrochlorotiazide
Appendix 2 shows that the average lowest unit price of treatment with combination products containing hydrochlorotiazide and eprosartan, valsartan, irbesartan, candesartan, telmisartan and olmesartan, respectively, is between DKK 6.42 and DKK 12.45, cf., however, the information below on high-strength combination products.

In comparison, the average lowest unit prices of combination products containing losartan and eligible for general reimbursement are between DKK 0.57 and DKK 1.89.

We emphasise the fact that the Committee in its recommendation of 29 March 2010 states that there is a class effect among all angiotensin II antagonists and that the medicinal products are recommended equally for all indications.

Combination products – high-strength hydrochlorotiazide and angiotensin II antagonists
No combination products containing losartan and hydrochlorothiazide have been marketed which in strength correspond to combination products containing hydrochlorothiazide and 320 mg valsartan and 32 mg candesartan, respectively, the lowest average unit prices of which are DKK 16.53 and DKK 16.75.

Regardless of the fact that combination products may support good compliance in the use of medicinal products, the Agency does not find that this circumstance in itself can justify a significantly higher price compared to a combination of a combination products containing losartan and hydrochlorotiazide and an individual substance product containing losartan taken separately. The total price is DKK 1.58 and DKK 2.64, respectively.

Combination products containing angiotensin II antagonists and, among others things, amlodipine
The average lowest unit price of combination products containing valsartan (80 mg and 160 mg) and amlodipine is between DKK 8.07 and DKK 10.40.

In comparison, the average lowest unit price of the individual substance product losartan is between DKK 0.62 and DKK 0.75. To this should be added DKK 0.32 and DKK 0.35, respectively, for amlodipine 5 and 10 mg.

The average lowest unit price of combination products containing valsartan (160 mg), amlodipine and hydrochlorothiazide is between DKK 11.66 and DKK 11.82. The average lowest unit price of combination products containing valsartan (320 mg), amlodipine and hydrochlorothiazide is DKK 16.76.

In comparison, the average lowest unit prices of combination products containing losartan and hydrochlorotiazide and eligible for general reimbursement are between DKK 0.83 and DKK 1.89. To this should be added DKK 0.32 and DKK 0.35, respectively, for amlodipine 5 and 10 mg.

The average lowest unit price of the combination product containing valsartan and amlodipine is thus significantly higher than the sum of the prices of the individual substance products containing losartan and amlopidine taken separately. Similarly, the average lowest unit price of combination products containing valsartan, amlodipine and hydrochlorothiazide is significantly higher than the average lowest unit price of combination prod-

ucts containing hydrochlorothiazide and losartan as well as amlodipine in separate formulations.

We believe that combination products may support good compliance in the use of medicinal products, but we do not find that this circumstance in itself can justify a significantly higher price compared to a combination of losartan and amlodipine taken separately and losartan/hydrochlorothiazide and amlodipine taken separately, respectively.

Against this background, the Agency finds that the relationship between the price of combination products containing eprosartan, valsartan, irbesartan, candesartan, telmisartan and olmesartan and their therapeutic value is not reasonable compared to medicinal products containing losartan.

With reference to section 144(2) of the Danish Health Act, the Agency is of the opinion that it is not possible to identify specific diseases or groups of people for which treatment with these medicinal products meets the criteria set out in the executive order on reimbursement for being granted general reimbursement (general conditional reimbursement), cf. section 1(2) of the executive order.

Re 1. and 2. – Medicinal products containing aliskiren
Appendix 2 shows that the average lowest price of treatment with individual substance products containing the renin inhibitor aliskiren is DKK 11.18 per day.

In comparison, the average lowest price of treatment per day for treatment with medicinal products containing the ACE inhibitors eligible for general reimbursement (enalapril, lisinopril, ramipril or trandolapril and the angiotensin II antagonist losartan) is between DKK 0.35 and DKK 2.20.

Appendix 2 also shows that the average lowest unit price of treatment with combination products containing aliskiren and hydrochlorotiazide is DKK 11.55.

In comparison, the average lowest unit prices of combination products containing the ACE inhibitors eligible for general reimbursement (enalapril, lisinopril or ramipril and the angiotensin II antagonist losartan, respectively) is between DKK 0.50 and DKK 1.89. To this should be added DKK 0.75 for 100 mg losartan, if relevant.

We emphasise the Committee's reference to the fact that medicinal products containing aliskiren should not be used except in cases where treatment with medicinal products eligible for general reimbursement acting on the renin-angiotensin system (medicinal products containing ACE inhibitors: enalapril, lisinopril, ramipril or trandolapril and the angiotensin II antagonist losartan) have been considered to be inadequate.

Against this background and with reference to the fact that aliskiren is recommended with provisos in the National Recommendation List as no clinical endpoint studies exist, the Agency finds that the relationship between the therapeutic value of medicinal products and the price is not reasonable.

Based on the same grounds, it is, in the opinion of the Agency, not possible to identify parts of the indication for these medicinal products which independently meet the criteria set out in the executive order on reimbursement for being granted general reimbursement (general conditional reimbursement).

With reference to section 1(3), item 5, of the executive order on reimbursement, the Agency also finds that general conditional reimbursement for those few cases entails the risk that aliskiren will be used as first-line treatment, even though this should not be the case in the opinion of the Agency. We do not find that any exceptional circumstances apply which may justify a different outcome.

In the exceptional circumstances in which treatment with medicinal products eligible for general reimbursement acting on the renin angiotensin system (medicinal products containing ACE inhibitors: enalapril, lisinopril, ramipril or trandolapril and the angiotensin II antagonist losartan) has shown to be inadequate, the general practitioner may apply for single reimbursement to the patient.

Legal framework
The legal basis for reassessment and withdrawal of reimbursement granted is sections 3 and 4 of Danish executive order no. 180 of 17 March 2005 on reimbursement and the principles laid down in the Danish Medicines Agency's guidelines of 8 June 2005 on the procedure for reassessment of the reimbursement status of medicinal products as well as the Danish Medicines Agency's guidelines of 4 July 2006 for assessment and comparison of medicinal products in connection with the reassessment of the reimbursement status of medicinal products. A link to these documents can be found at www.dkma.dk > Companies > General reimbursement > Reassessment of reimbursement status for medicinal products (the fact box). A link to the Danish executive order on reimbursement can be found here: http://lms-lw.lovportaler.dk/ShowDoc.aspx?docId=bek20050180-full. A link to the Danish Health Act can be found here: http://lms-lw.lovportaler.dk/showdoc.aspx?docId=lov20050546.

Reassessment
In connection with the introduction of reassessments of the reimbursement status of medicinal products in 2005, it was decided that the reimbursement status of all medicinal products should be reassessed regularly. Therefore,

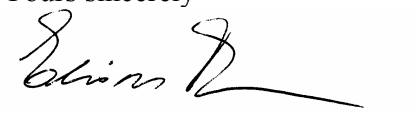
the reimbursement status of the medicinal products will be assessed again as part of this regular reassessment procedure.

In addition, the Danish Medicines Agency can initiate ad hoc reassessments, e.g. when we receive important new information about inappropriate consumption, new treatment recommendations, significant price changes etc. The Agency monitors the development in the consumption and prices of medicinal products comprised by this decision.

Complaints
This decision may be appealed to the Danish Ministry of Interior and Health, Slotsholmsgade 10-12, 1216 Copenhagen K, Denmark. However, the Ministry cannot reassess the Danish Medicines Agency's scientific estimate.

Information
Doctors and pharmacies will be informed of the content of this decision via articles in professional journals and letters from the Danish Medicines Agency etc. Other stakeholders will receive a notification referring to the Agency's website. The decision, various information material and an overview of the current and future reimbursement status of all medicinal products comprised by this decision will be available at the website. Furthermore, we will ask pharmacies to hand out an information sheet on the changes to the affected patients.

Yours sincerely



Elisabeth Thomsen

Appendix 1: Note on consultation on proposals for future reimbursement status of medicinal products for cardiovascular diseases in ATC groups C09C, C09D and C09X.
Appendix 2: Price survey

Danish Medicines Agency
Case no. 5315-2
11 June 2010

Appendix 1 – Note on consultation on proposal for future reimbursement status of medicinal products for cardiovascular diseases in ATC groups C09C, C09D and C09X

Parties to the consultation

Concerned companies:
2care4 ApS, AstraZeneca A/S, Bayer AG-Leverkusen, Bayer Schering Pharma AG, Boehringer Ingelheim, Boehringer Ingelheim Pharma GmbH, Bristol-Myers Squibb Pharma EEIG, Daiichi Sankyo Europe GmbH, EuroPharmaDK ApS, Menarini International Operation, Merck Sharp & Dohme BV, Novartis Europharm Ltd., Novartis Healthcare A/S, Orifarm A/S, Paranova Danmark A/S, PharmaCoDane ApS, Sanofi Pharma Bristol-Meyers, Sanofi Pharma Bristol-Myers, Singad Pharma ApS, Solvay Pharmaceutical GmbH and Solvay Pharmaceuticals B.V.

Medical 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 Danish Society of Obstetrics and Gynaecology.

Patient organisations:
Danish Patients, Disabled Peoples' Organisations Denmark, Danish Heart Foundation, Danish Diabetes Association and Danish Stroke Association.

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

The Danish Medicines Agency has received 12 consultation responses. A link to the responses can be found here: http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=17332

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 meeting on 18 May 2010, and the Committee found no reason to alter or add comments to its recommendation.

This note makes reference to important points stated in the consultation responses received and contains the comments of the Agency thereon.

1. Process flow
A number of parties to the consultation criticise the fact that the proposed reimbursement amendment is presented so soon after the latest reimbursement amendment in ATC group C09.

The introduction of the regular reassessment of the reimbursement status of all medicinal products was based on the precondition that a periodic review of the entire range of medicinal products must be

performed. Another precondition was that important changes in the preconditions for general reimbursement could trigger a so-called ad hoc reassessment and that the possibility of withdrawing a decision on general reimbursement should continue to exist after the preconditions for this decision no longer exist. This possibility is also described in the Danish Medicines Agency's decision of 16 January 2009, in which the Agency made the general reimbursement for angiotensin II antagonists conditional: "In connection with the introduction of the reassessment of the reimbursement status of medicinal products in 2005, it was decided that the reimbursement status of all medicinal products must be reassessed regularly. The reimbursement status granted to the medicinal products following this decision will thus be reassessed in connection with this regular reassessment procedure. In addition, the Agency can initiate ad hoc reassessments, e.g. when we receive new information about inappropriate consumption, new treatment recommendations, changes in price etc. The Agency monitors the development in the consumption and prices of medicinal products comprised by this decision."

It is correct that we, in our letter to the companies in June 2005 under the heading "Systematic, periodic reassessment of the reimbursement status of medicinal products" stated that the companies would have three months to submit any comments. This reassessment of the reimbursement status does, however, not take place as part of the regular periodic reassessment, but constitutes an ad hoc reassessment which is carried out in exceptional cases, e.g. as a result of significant price reductions due to the introduction of generics containing losartan, which is the case here, cf. also the Agency's guidelines of 8 June 2005 on the procedure for reassessments: http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=6306. As this area of therapy has just been reviewed as part of the regular reassessment of the reimbursement status of medicinal products, and as the Reimbursement Committee's recommendation of 29 March 2010 is based materially on the Committee's recommendations on which the Agency's decision of 16 January 2009 was based, we find that a time-limit of five weeks gives the affected parties a reasonable amount of time to familiarise themselves with the information and consider their statement.

2. Financial implications for the research industry
Several parties to the consultation want the Danish Medicines Agency to consider the long-term, negative derived implications of the reassessment for the continuous research in and development of new treatment options as well as for the further training of healthcare professionals, and they question the fact that the change will result in public cost savings.

The purpose of the rules on reimbursement contained in the Danish Health Act is to provide public subsidies for medical treatment and to ensure an appropriate allocation of the funds of the regions and encourage rational use of medicinal products. The above-mentioned considerations for the research industry do not constitute statutory criteria which may be included in the Agency's decisions on reimbursement for medicinal products. In addition, the purpose of reassessing the reimbursement status of medicinal products is not to cut costs, but to ensure that the medicinal products meet the criteria for general reimbursement.

3. Documentation – approved indications
Several parties to the consultation state that losartan has not been documented to the same extent as the other angiotensin II antagonists, including for heart insufficiency, in respect of which valsartan and candesartan are particularly noteworthy.
The documentation is not equally extensive, but we refer to the fact that the medicinal products are recommended equally for all indications in both national and international treatment guidelines, cf. also the Reimbursement Committee's recommendation of 29 March 2010.

The Danish Society of Nephrology states that angiotensin II antagonists other than losartan, as a general rule, can be given once a day and thus have a well-defined place in therapy. The Danish Society of

Cardiology refers to data on, e.g., losartan, candesartan and valsartan and points out that candesartan and valsartan are well-documented in the treatment of heart insufficiency. The Society also states that the changed reimbursement rules, in its opinion, may result in a material deterioration of the treatment of heart insufficiency if patients are switched to losartan 50 mg, which, according to the Society, is incorporated in clinical practice. The Society recommends that valsartan and candesartan maintain their general conditional reimbursement when the reimbursement status of losartan is changed from general conditional reimbursement to general reimbursement.

We place emphasis on the Reimbursement Committee's reference to the National Recommendation List for medicinal products acting on the renin angiotensin system (C09), which states: "The effect of the angiotensin 2 antagonists is deemed to constitute a class effect for all relevant indications even though not all substances are documented to the same extent in clinical endpoint studies. Several substances (candesartan, losartan and valsartan) have the recorded indication heart insufficiency. As there are no other circumstances which seem to separate the effect and adverse reactions of the different angiotensin 2 antagonists, the specialist group and the steering group believe that a class effect exist." (http://www.irf.dk/dk/rekommandationsliste/baggrundsnotater/hjerte_og_kredsloeb/c09_midler_til_renin-angiotensin_systemet.htm). Both the Danish Society of Nephrology and the Danish Society of Cardiology were represented in the expert group in connection with the work on the National Recommendation List.

The Agency also emphasises the Committee's reference to the Danish Hypertension Society's treatment guidelines from 2009 (http://www.dahs.dk/fileadmin/Behandlingsvejled0910-endelig-printversion.pdf), in which the angiotensin II antagonists are classified as equal (page 5 and page 8, where kidney disease is mentioned).

We consider the reimbursement status of a medicinal product and not regimens, e.g. the choice between 50 mg and higher doses of losartan. That is the responsibility of the treating general practitioner.

Boehringer Ingelheim states that the Committee has stated a wrong indication in Appendix B. It is correct that the approved indication stated in Appendix B to the Committee's recommendation of 29 March 2010 is incomplete, but we refer to the fact that, according to the National Recommendation List, angiotensin II antagonists are recommended equally. The On-Target study to which the company refers is a reference to the National Recommendation List (source 24).

Sanofi Aventis states that irbesartan has a better 24-hour coverage in the treatment of hypertension than losartan, and AstraZeneca refers to a meta-analysis of randomised studies which have shown a better blood pressure reduction on different regimens of candesartan compared to different regimens of losartan.
In line with the Committee, we generally focus on the effect on clinically significant endpoints.

AstraZeneca refers to recent Swedish data stating that the mortality for candesartan is 14% lower than for losartan, and that 50% excess mortality has been shown for treatment with losartan compared with candesartan in patients suffering from heart insufficiency. The Agency agrees that observational studies are interesting and important, e.g. when it comes to the study of rare adverse reactions, but such studies are retrospective, observational, non-randomised studies which, in our opinion, cannot be used for determining differences in effect of the above-mentioned size. We note that these new studies have not given rise to a change of the Committee's recommendation of 29 March 2010.

Finally, AstraZeneca refers to pharmacoeconomic studies which compare candesartan with generic losartan – i.e. losartan at the original price. The financial comparisons, which showed a larger resource

consumption among patients treated with losartan, are based on retrospective, observational, non-randomised studies. This difference is caused by a higher number of outpatient consultations. The estimated financial difference disappears if the price of losartan is reduced by 90%, corresponding to the decrease in the price of losartan. Furthermore, we believe that the difference in effect is far too small to determine whether there is a real difference due to the observational design.

4. Comparison of analogue medicinal products in relation to reimbursement
The Danish Association of the Pharmaceutical Industry states that general comparisons between products with different active substances and different documentation involves an unsubtle average consideration of both product variations and the very diversified patient population of hypertonics.

Novartis states that the Committee's recommendation is based on a simplified view on the possibilities of effective treatment as the different effects of the medicinal products on different indications have not been taken into consideration. Novartis argues that the information in the Committee's recommendation is incomplete as clinical differences in the therapeutic effect of the medicinal products have not been considered.

The Committee's recommendation of 29 March 2010 is, just like the Committee's recommendations of 29 January 2008 and 2 September 2008, based on the fact that neither national nor international treatment guidelines question the fact that a class effect exists among the angiotensin II antagonists and that they are recommended equally for all indications. We agree that aliskiren differs from the angiotensin II antagonists, but, given the price of aliskiren, we do not believe that this difference is large enough to justify a difference in reimbursement status. In this connection, we note that, in the National Recommendation List, aliskiren is recommended with provisos as no clinical endpoint studies exist. On the basis of these evidence-based references, we do not believe that the Committee's recommendation constitutes unsubtle average considerations or simplified views on optimum treatment, nor that the information in the Committee's recommendation is incomplete.

Novartis states that it is difficult to understand that the Danish Medicines Agency in one department strictly enforces the ban to promote medicinal products outside the indication area by pharmaceutical companies when the Committee groups the medicinal products without consideration being given to the different indications.

In these two situations, the Agency is subject to two different sets of rules, namely the advertising rules in the Danish Medicines Act and the reimbursement rules in the Danish Health Act.
The comments to the act to amend the Danish Health Service Act and the Danish Social Service Act, published as Act no. 1045 of 23 December 1998, today replaced by the Danish Health Act (http://lms-lw.lovportaler.dk/ShowDoc.aspx?docId=lov20050546#p143), 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 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 medicinal products. Therefore, the fact that a medicinal product has not been granted reimbursement, cannot be interpreted to mean that it is less effective, less safe or of poorer quality than medicinal products with reimbursement."

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

5. Change of conditional reimbursement
Novartis states that the introduction of generic competition cannot justify that it will no longer be possible to prescribe medicinal products containing valsartan or aliskiren to patients with specific treatment needs.

As valsartan, with reference to the class effect with losartan, and aliskiren, with reference to the fact that the medicinal product should not be used except in cases where treatment with medicinal products eligible for general reimbursement acting on the renin-angiotensin system (medicinal products containing ACE inhibitors: enalapril, lisinopril, ramipril or trandolapril and the angiotensin II antagonist losartan) have been considered to be inadequate, the Agency finds that the number of patients with a specific need for treatment with valsartan or aliskiren is very limited and should be administered under the single reimbursement scheme.

6. Change of medicine
Many parties to the consultation state that the change of medicine which will be a natural result of the reimbursement change may be a burden to both the general practitioner and the patient. The Danish Medicines Agency acknowledges that switching to another treatment may be a burden to both the general practitioner and the patient. The change in the reimbursement status of the medicinal products is thus implemented giving five months' notice and is accompanied by considerable information efforts towards general practitioners, pharmacies and patients. See also the section "Compliance" below.

7. Compliance
Several parties to the consultation point out that compliance in connection with a change of product constitutes an important problem.
We presuppose that general practitioners perform changes of product under close monitoring and with respect for the patient's overall pathological picture and treatment. We hold 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.

The Danish Hypertension Society states that the reimbursement for a number of useful combination products will be removed, resulting in a possible deterioration of patient compliance.
Novartis states that the Danish Medicines Agency is under an obligation to ensure that considerations for compliance are included in the decision.

We must assess whether the relationship between the therapeutic value of a medicinal product and its price is reasonable. In its assessment of the therapeutic value of a medicinal product, the Agency may include the consideration for compliance. We have included the consideration for compliance, but agree with the Reimbursement Committee that this consideration cannot justify the difference in the prices of the medicinal products in question and losartan and the ACE inhibitors eligible for general reimbursement, respectively. In addition, it is likely that lower treatment expenses resulting from a change of product will improve the patient's compliance. The Agency believes that the increased focus on these patients in connection with a switch to another medicine will contribute to diminishing undertreatment and ensuring a greater extent of adequate treatment.

8. Financial impact analysis
Several parties to the consultation request a financial impact analysis.

The Danish Association of the Pharmaceutical Industry states that each patient should contact his or her general practitioner twice to have his or her changed treatment adapted, which involves a hidden resource consumption for both the general practitioner and the patient.

It has not been a precondition that the Danish Medicines Agency was to perform a health economic assessment of the impact of reimbursement changes in relation to reassessment. The financial impact 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 question was examined by the Danish Ministry of Health and Prevention in its decision concerning Servier Danmark A/S's complaint about the Agency's decision of 16 January 2009. In its decision, the Ministry stated:
"Against this background, the Ministry does not find that the Danish Medicines Agency, in it reassessment of ACE inhibitors, including its decision to change the reimbursement status of Servier's Coversyl products as well as Coversical, has disregarded aspects – an analysis of the socioeconomic impact of a change of product – which the Agency was required to include in its reassessment."
A link to the decision can be found here:
http://www.laegemiddelstyrelsen.dk/db/filarkiv/7839/Captia_Besvarelse_af_klage.pdf

9. Changes to the established therapy
Several parties to the consultation recommend that no changes be made to the established therapy.
The main criteria for granting general reimbursement is that the medicinal product has a safe and beneficial effect on a clearly defined indication, and that the relationship between the price of the medicinal product and its therapeutic value is reasonable. In cases where the Danish Medicines Agency finds that the criteria for granting general reimbursement for a medicinal product have not been met for the medicinal product's entire spectrum of use, including for all the indications for which the medicinal product has been approved, the Agency automatically assesses whether the criteria have been met on the condition that the medicinal product is prescribed with a view to treating specific diseases or groups of people (general conditional reimbursement). In our opinion, the inconveniences associated with a change of product are not so important that the therapeutic value of such medicinal products for the group of patients already in treatment with these medicinal products outweighs the large price difference. Therefore, we do not find that the criteria for a general conditional reimbursement have been met for persons in treatment with one of the expensive angiotensin II antagonists.

10. Considerations regarding patents
Several parties to the consultation criticise the Danish Medicines Agency's ad hoc reassessment of the angiotensin II antagonists, referring to the fact that the patents for valsartan and candesartan are to expire at the end of 2011 and the patent for irbesartran is to expire in 2012.
The Agency assesses whether the relationship between the therapeutic value of a medicinal product and its price is reasonable, cf. section 1(1), item 2, of the executive order on reimbursement. The basis for decision on the reimbursement status of a medicinal product does not contain any legal base for including the patent status of a medicinal product, and any future price decreases due to patent expiries do no form part of the Agency's basis for decision.

11. Fee for single reimbursement application
AstraZeneca states that general practitioners charge a fee for single reimbursement applications and that the patient thus incurs increased expenses. It is correct that general practitioners may charge a fee for single reimbursement applications.

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Price survey for medicinal products, single substance products and combination products in ATC groups C09C, C09D and C09X and relevant comparable medicinal products for six price periods (for the period 8 March 2010 to 17 May 2010)

Re single substance products: Average lowest price of treatment for hypertension per day, calculated over six price periods.
Re combination products: Average lowest unit price, calculated over six price periods.

Single substance products

ATC	Active substance/ group	DDD (mg)	Dose used (mg)[1]	Pharmaceutical form	Strength(s) (mg)	Average lowest unit price(s) (DKK)	Treatment price per day (DKK)
C09CA	**Angiotensin II antagonists, plain**						
C09CA01	Losartan	50	50 - 100 [4 5]	Film-coated tablets	50 / 100	0.62 / 0.75	0.62 - 0.75
		50	50 - 100	Powd. + solv. for oral susp	2.5 mg/ml	2.90 DKK/ml	58.00 - 116.00
C09CA02	Eprosartan	600	600 [4 5]	Film-coated tablets	600	6.41	6.41
C09CA03	Valsartan	80	80 - 160 [4 5]	Film-coated tablets	80 / 160	7.86 / 10.92	7.86 - 10.92
C09CA04	Irbesartan	150	150 - 300 [4 5]	Tablets/film-coated tablets	150 / 300	7.31 / 9.22	7.31 - 9.22
C09CA06	Candesartan	8	8 - 16 [4 5]	Tablets	8 / 16	5.29 / 6.72	5.29 - 6.72
C09CA07	Telmisartan	40	40 - 80 [4 5]	Tablets	40 / 80	7.35 / 8.76	7.35 - 8.76
C09CA08	Olmesartanmedoxomil	20	20 - 40 [4 5]	Film-coated tablets	20 / 40	6.42 / 7.74	6.42 - 7.74
C09XA	**Renin inhibitors**						
C09XA02	Aliskiren	150	150 [3 6]	Film-coated tablets	150 / 300	11.18 / 11.55	11.18
C09AA	**ACE inhibitors, plain**						
C09AA01	Captopril	50	50 [2 3 7]	Tablets	25	0.39	0.78
C09AA02	Enalapril	10	20 - 40 [4 5]	Tablets	20	0.37	0.37 - 0.74
C09AA03	Lisinopril	10	20 [4 5]	Tablets	20	0.75	0.75
C09AA05	Ramipril	2.5	5 - 10 [4 5]	Tablets/capsules/film-coate	5 / 10	0.35 / 0.66	0.35 - 0.66
C09AA10	Trandolapril	2	4 [4 5]	Capsules/hard capsules	2	1.10	2.20

Combination products

ATC	Active substance/group	Pharmaceutical form	Strength(s) (mg)	Average lowest unit price(s) (DKK)
C09DA	**Angiotensin II antagonists and diuretics**			
C09DA01	Losartan and hydrochlorothiazide	Film-coated tablets	50+12.5 / 100+12.5	0.57 / 1.89 and 12.48 [8]
			100+25	0.83
C09DA02	Eprosartan and hydrochlorothiazide	Film-coated tablets	600 + 12.5	6.62
C09DA03	Valsartan and hydrochlorothiazide	Film-coated tablets	80+12.5 / 160+12.5	7.86 / 10.00
			160+25 / 320+12.5	9.10 / 16.53
			320+25	16.53
C09DA04	Irbesartan and hydrochlorothiazide	Tablets/film-coated tablets	150+12.5 / 300+12.5	6.73 / 8.39
			300+25	12.45
C09DA06	Candesartan and hydrochlorothiazid	Tablets	8+12.5 / 16+12.5	7.41 / 9.01
			32+12.5 32+25	16.75 / 16.75
C09DA07	Telmisartan and hydrochlorothiazide	Tablets	40+12.5 80+12.5	7.67 / 7.63
			80+25	11.92
C09DA08	Olmesartan and hydrochlorothiazide	Film-coated tablets	20+12.5 20+25	6.42 / 6.42
C09DB	**Angiotensin II antagonists and calcium channel blockers**			
C09DB01	Valsartan and amlodipine	Film-coated tablets	80+5 / 160+10	8.07 / 10.31
			160 + 5	10.40 /
C08CA01	Amlodipine	Tablets	5 / 10	0.35 / 0.32
C09DX	**Angiotensin II antagonists, other combinations**			
C09DX01	Valsartan, amlodipine and HCT	Film-coated tablets	160+5+12.5 / 160+10+12.5	11.66 / 11.82
			160+5+25 / 160+10+25	11.66 / 11.82
			320+10+25	16.76
C08CA01	Amlodipine	Tablets	5 / 10	0.35 / 0.32
C09XA	**Renin inhibitors**			
C09XA52	Aliskiren and hydrochlorothiazide	Film-coated tablets	150+12.5 / 150+25	11.55 / 11.55
			300+12.5 / 300+25	11.55 / 11.55
C09BA	**ACE inhibitors and diuretics**			

C09BA02	Enalapril and hydrochlorothiazide	Tablets	20+12.5	0.50
C09BA03	Lisinopril and hydrochlorothiazide	Tablets	10+12.5 / 20+12.5	0.61 / 0.91
C09BA05	Ramipril and hydrochlorothiazide	Tablets	5+25	0.73

Notes/explanations:

1	Unless otherwise stated, the dose can be given once a day
2	Divided into two daily doses
3	DDD value (WHO)
4	Equieffective dose for the treatment of hypertension from the National Recommendation List (IRF), 12 January 2009
5	Recommended in the National Recommendation List (IRF), 12 January 2009
6	Recommended with provisos in the National Recommendation List (IRF), 12 January 2009
7	Not recommended in the National Recommendation List (IRF), 12 January 2009
8	Not all medicinal products in this strength belong to the same substitution group