For companies which as of 1 December 2008 or before notified a price of one or more medicinal products approved for marketing in ATC group C08

Decision on future reimbursement status for medicinal products in ATC group C08 as a result of the reassessment process

16 January 2009

Case no.:
5315-9

With this decision, the Danish Medicines Agency concludes the reassessment of the reimbursement status for medicinal products in ATC group C08 (calcium channel blockers).

The decision is an overall decision on the reimbursement status **as of 13 July 2009**[1] for all medicinal products of all strengths (unless otherwise stated) in ATC group C08, for which a price is or has been notified to the Danish Medicines Agency as of 1 December 2008 or before.

Presentation
The Reimbursement Committee has submitted two recommendations containing the Committee's recommendations for the future reimbursement status for medicinal products in ATC groups C02 (antihypertensives), C03 (diuretics), C07 (beta blocking agents), C08 (calcium channel blockers) and C09 (ACE inhibitors, angiotensin II antagonists and renin inhibitors). The first recommendation is dated 29 January 2008. The additional recommendation is dated 2 September 2008. The Committee's recommendations are available at www.dkma.dk > Companies > General reimbursement > Reassessment of reimbursement status for medicinal products, notifications of 14 February and 9 September 2008.

The recommendations of the Reimbursement Committee have been submitted to the affected companies, scientific societies, patient organisations etc. for consultation. Furthermore, we have carried out a hearing with updated prices for medicinal products containing the individual substances isradipine (C08CA03), nifedipine (C08CA05), nitrendipine (C08CA08), lacidipine (C08CA09) and lercanidipine (C08CA13) as well as for combination products containing verapamil and trandolapril (C08DA51).

Please see the consultation memorandum enclosed as **Appendix 1** for the most important viewpoints stated in the consultation responses and the Danish Medicines Agency's comments thereon.

[1] Cf., however, item 3 on nimodipine (C08CA06)

The decision made, the grounds therefore, the regulatory framework and the complaint instructions are stated below.

Decision

1. Oral medicinal products in ATC group C08 containing the individual substances

- amlodipine (C08CA01)
- felodipine (C08CA02)
- verapamil (C08DA01)
- diltiazem (C08DB01)

maintain their current reimbursement status (general reimbursement) as of 13 July 2009.

The Danish Medicines Agency finds that these medicinal products still *meet* the criteria for being granted general reimbursement, cf. section 1(2) of the executive order on reimbursement[2].

2. Oral medicinal products in ATC group C08 containing the individual substances

- isradipine (C08CA03)
- nifedipine (C08CA05)
- nitrendipine (C08CA08)
- lacidipine (C08CA09)
- lercanidipine (C08CA13)

will as of 13 July 2009 have their reimbursement status changed to general conditional reimbursement with the condition:

"Patients with hypertension or any other type of cardiovascular disease requiring treatment where treatment with dihydropyridine calcium channel blockers eligible for general unconditional reimbursement

- is not tolerated, or
- in exceptional cases has been deemed inappropriate by a doctor based on an overall clinical assessment of the patient's condition."

With reference to section 1(2), item 2 of the executive order on reimbursement, in relation to the question of general reimbursement, the Danish Medicines Agency finds that the relationship between the price of the medicinal products and their therapeutic value is not reasonable when comparing the medicinal products in question with amlodipine and felodipine. With reference to section 1(3), item 5 of the executive order on

[2] Danish executive order no. 180 of 17 March 2005 on reimbursement, as amended

reimbursement, the Danish Medicines Agency also finds that there is a risk that the medicinal products in question will be used as first-line treatment, even though this should not be the case in the opinion of the Danish Medicines Agency. We do not find that any exceptional circumstances apply which could provide the basis for another result.

In relation to the question of general conditional reimbursement, the Danish Medicines Agency finds, with reference to section 1(4) of the executive order on reimbursement, that the medicinal products in question within the above condition *meet* the criteria for being granted general reimbursement, cf. section 1(2), item 2 of the executive order on reimbursement.

3. Oral medicinal products in ATC group C08 containing the individual substance

- nimodipine (C08CA06)

will as of 9 February 2009 have their reimbursement status changed and will be granted general reimbursement.

The Danish Medicines Agency finds that these medicinal products *meet* the criteria for being granted general reimbursement, cf. section 1(2) of the executive order on reimbursement.

Oral combination products in ATC group C08 containing

- verapamil and trandolapril (C08DA51)

will as of 13 July 2009 have their reimbursement status changed and will not be granted general reimbursement.

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

With reference to section 1(4) of the executive order on reimbursement, it is, in the opinion of the Danish Medicines Agency, not possible to identify parts of the indication ('specific diseases') 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).

5. Infusion fluids and injection products in ATC group C08 containing

- nimodipine (C08CA06)
- verapamil (C08DA01)

maintain their reimbursement status and will as of 13 July 2009 not be granted general reimbursement.

The Danish Medicines Agency finds that these medicinal products are comprised by the exception set out in section 1(3), item 8 of the executive order on reimbursement. In the opinion of the Danish Medicines Agency, the medicinal products are primarily used in hospital treatment and we do not find that any exceptional circumstances apply which could provide the basis for another result.

Grounds
In its recommendation of 29 January 2008, the Reimbursement Committee stated that, based on an overall assessment, the use of the calcium channel blockers with a majority of the consumption being the cheaper substances amlodipine and felopidine was appropriate, and the Committee thus recommended that the calcium channel blockers eligible for general reimbursement maintain their general reimbursement status.

The Reimbursement Committee's additional recommendation of 2 September 2008 was based on the assumption that the Danish Medicines Agency will include any changes in price and consumption occurring after the Committee submitted its first recommendation on 29 January 2008 in its assessment basis.

Appendix II/C08 contains an updated price and consumption list for individual substances in ATC group C08 specifying the average lowest prices of treatment per day, the consumption at active substance level as well as the names and pharmaceutical forms of all medicinal products comprised by this decision. The prices of treatment per day are calculated over six price periods for the period 22 September 2008 to 14 December 2008. For these medicinal products, the dose used is established on the basis of the indication of hypertension.
Appendix III/C08 contains an updated price and consumption list specifying the average lowest unit prices calculated over the same period for combination products in ATC group C08 and for the individual substances of similar strength and in relevant comparable pharmaceutical form.

The prices on which the decision is based are calculated in accordance with the Danish Medicines Agency's guidelines of 4 July 2006 for evaluation and comparison of medicinal products in reassessments of reimbursement status, cf. below under Regulatory framework.

Changes in price and consumption which have occurred after 1 December 2008 do not give rise to a changed assessment, cf. below.

Re 1 and 2 – Individual substances for oral treatment excl. nimodipine
At the time of the Reimbursement Committee's recommendation, the price of treatment per day for oral treatment with the individual substances in ATC group C08CA (dihydropyridine calcium channel blockers excl.

nimodipine) was between DKK 0.90 to DKK 8.90 stated at reimbursement prices.

Appendix II/C08 shows that the average lowest price of treatment per day for oral treatment with the individual substances amlodipine and felodipine is now between DKK 0.26 and DKK 0.58.

By comparison, the average lowest price of treatment per day for oral treatment with the individual substances isradipine, nifedipine, nitrendipine, lacidipine and lercanidipine is between DKK 2.79 and DKK 9.52.

The Danish Medicines Agency emphasises the Reimbursement Committee's medical assessment of the medicinal products and their use, which is expressed in the Reimbursement Committee's recommendation of 29 January 2008.

As for the dihydropyridine calcium channel blockers, patients requiring treatment with these medicinal products should, in our opinion, be treated with the cheaper dihydropyridine calcium channel blockers amlodipine and felodipine as first-line treatment, and, in relation to isradipine, nifedipine, nitrendipine, lacidipine and lercanidipinin, there is, in our opinion, a risk that the medicinal products in question will be used as first-line treatment in cases where this should not be the case.

The Danish Medicines Agency recognises that some patients may require other treatment options than amlodipine or felodipine due to adverse reactions, including, amongst others, ankle oedema or interactions caused by these substances or – with respect to nifedipine – for the treatment of Raynaud's phenomenon. The reimbursement condition allows for this. For these patients, the doctor has to write 'tilskud' (reimbursement) on the prescription.

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

Re 3 – Individual substances for oral treatment – nimodipine
As for nimodipine, the Danish Medicines Agency emphasises the opinion of the Reimbursement Committee that the medicinal product has its specific place in the treatment for the prevention and treatment of spasms in subarachnoidal haemorrhage caused by a burst aneurysm, and that there is no risk that it will be used inappropriately outside this indication.

The price of treatment and the consumption of nimodipine are at the same level as the consumption on which the Committee based its recommendation of 29 January 2008.

Re 4 – Combination products for oral treatment
As the basis of our assessment of the future reimbursement status for combination products in ATC group C08, we have, taking the actual marketed strengths and pharmaceutical forms of the combination products in question as our point of departure, calculated the average lowest unit price for the combination product and the individual substances, respectively, of similar strength and in relevant comparable pharmaceutical form. Please see **Appendix III/C08**.

Appendix III/C08 shows that the average lowest unit price for combination products containing verapamil and trandolapril is between DKK 7.06 and DKK 9.36. The average lowest unit price of the individual substances is DKK 0.87 to DKK 2.72 for verapamil and DKK 0.67 for trandolapril.

The Danish Medicines Agency agrees with the Reimbursement Committee that combination products may support good compliance in the use of medicinal products, but we do not, however, find that the high price of the combination of verapamil and trandolapril can be justified. The Danish Medicines Agency does thus not find that the relationship between the price of the medicinal products and their therapeutic value is reasonable.

Re 5 – Infusion fluids and injection products
The Danish Medicines Agency emphasises what the Reimbursement Committee stated in relation to infusion fluids and injection products in ATC group C08 in the Committee's recommendation of 29 January 2008, viz. that these medicinal products are exclusively used in hospitals and thus should not be granted general reimbursement.

Regulatory 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 in accordance with 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 evaluation and comparison of medicinal products in reassessments of reimbursement status. 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).

Reassessment
In connection with the introduction of the reassessment of the reimbursement status of medicinal products in 2005, it was decided that the

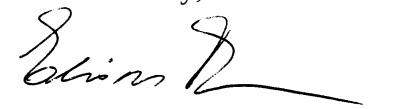
reimbursement status of all medicinal products should be reassessed regularly. The reimbursement status granted to the medicinal products following this decision will thus be reassessed in connection with this regular reassessment procedure.

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

Information
Doctors and pharmacies will be informed of the content of this decision via articles in professional journals etc. Other stakeholders will receive a notification referring to the Danish Medicines Agency's website. All decisions with appendices for medicinal products in ATC groups C02, C03, C07, C08 and C09 as well as an overview of the current and future reimbursement status for all medicinal products comprised by these decisions will be available at the website.

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

Yours sincerely,



Elisabeth Thomsen

Appendix II/C08: Price and consumption list of calcium channel blockers, individual substances

Average lowest price of treatment per day for hypertension calculated over six price periods (for the period 22 September to 14 December 2008)

1. ATC	2. Active substance/ group	3. Number of persons treated 2006	2007	4. Dose used (mg)[1]		5. Pharmaceutic. form	6. Strength(s) (mg)	8. Avg. lowest unit price(s) (DKK)	8. Avg. lowest price of treat. per day (DKK)
C08CA	**Dihydropyridine deriv.**	229,036	258,778						
C08CA01	Amlodipine	174,749	203,181	5 - 10	45	Tablets	5 / 10	0.26 / 0.32	0.26 - 0.32
C08CA02	Felodipine	33,798	33,704	5 - 10	45	Prolonged-rel. tab.	5 / 10	0.45 / 0.58	0.45 - 0.58
C08CA03	Isradipine	2,181	2,102	5 - 10	45	Prol.-rel. cap., hard	5	4.76	4.76 - 9.52
C08CA05	Nifedipine	11,330	10,930	30 - 120	45	Prolonged-rel. tab.	30 / 60	3.11 / 4.48	3.11 - 8.96
		11,330	10,930	30 - 120	467	Tablets	10	1.86	5.58
		11,330	10,930	30 - 120	467	Caps./film-coat. tab	10 / 20	0.93 / 2.18	2.79 - 11.16
C08CA06	Nimodipine	45	26	300	368	Film-coated tablets	30	6.49	64.90
		45	26	50	36	Infusion fluid	0.2 mg/ml	5.05 DKK/ml	1262.50
C08CA08	Nitrendipine	740	682	10 - 20	45	Tablets	10 / 20	3.34 / 4.86	3.34 - 4.86
C08CA09	Lacidipine	1,988	1,980	2 - 4	45	Tab/film-coat. tab	2 / 4	5.31 / 7.35	5.31 - 7.35
C08CA13	Lercanidipine	7,850	10,374	10 - 20	45	Film-coated tablets	10 / 20	3.47 / 5.34	3.47 - 5.34
C08DA	**Phenylalkylamine deriv.**	29,702	28,566						
C08DA01	Verapamil	28,985	27,929	240 - 480	245	Prol.-rel. cap., hard	120 / 240	1.53 / 2.72	3.06 - 5.44
		28,985	27,929	240 - 480	245	Prolonged-rel. tab.	120 / 240	1.59 / 0.87	3.18 - 1.74
		28,985	27,929	240 - 480	458	Film-coated tab./tab.	80 / 120	0.64 / 0.63	1.92 - 2.52
		28,985	27,929	240	3	Injection fluid	2.5 mg/ml	4.59 DKK/ml	440.64
C08DB	**Benzothiazepine deriv.**	16,028	14,641						
C08DB01	Diltiazem	16,028	14,641	180 - 360	245	Prolonged-rel. tab.	60 / 180	1.90 / 7.63	5.70 - 15.26
		16,028	14,641	180 - 360	459	Film-coated tablets	60	1.54	4.62 - 9.24

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 from IRF's background note
5	Recommended by IRF
6	Not recommended by IRF
7	Divided into three daily doses
8	Divided into six daily doses
9	Divided into 3-4 daily doses

Name and form of medicinal product

ATC	Name	Form
C08CA01	Amlodipine '1A Farma'	tablets
	Amlodipine 'Actavis'	tablets
	Amlodipine 'Alternova'	tablets
	Amlodipine 'BMM Pharma'	tablets
	Amlodipine 'Copyfarm'	tablets
	Amlodipine 'GEA'	tablets
	Amlodipine 'Hexal'	tablets
	Amlodipine 'Krka'	tablets
	Amlodipine 'Orion'	tablets
	Amlodipine 'PCD'	tablets
	Amlodipine 'Ranbaxy'	tablets
	Amlodipine 'ratiopharm'	tablets
	Amlodipine 'Sandoz'	tablets
	Amlovis	tablets
	Norvasc	tablets
C08CA02	Felodine	prolonged-release tablets
	Felodipine 'Actavis'	prolonged-release tablets
	Felodipine 'HEXAL'	prolonged-release tablets
	Felodipine 'ratiopharm'	prolonged-release tablets
	Felodipine 'Sandoz'	prolonged-release tablets
	Felodipine Retard '1A Farma	prolonged-release tablets
	Hydac	prolonged-release tablets
	Plendil	prolonged-release tablets
	Plendur	prolonged-release tablets
C08CA03	Lomir Retard	prolonged-release capsules, hard
C08CA05	Adalat	tablets

	Adalat Oros	prolonged-release tablets
	Hexadilat	film-coated tablets
	Hexadilat	capsules, soft
	Nifecodan	film-coated tablets
	Nifedipine ‘Alternova’	prolonged-release tablets
	Nifedipine ‘NM’	film-coated tablets
C08CA06	Nimotop	film-coated tablets
	Nimotop	infusion fluid
C08CA08	Baypress	tablets
C08CA09	Midotens	tablets
	Motens	film-coated tablets
C08CA13	Zanedip	film-coated tablets
	Zanidip	film-coated tablets
C08DA01	Hexasoptin	coated tablets
	Hexasoptin Retard	prolonged-release capsules, hard
	Isoptin Retard	prolonged-release tablets
	Veraloc	injection fluid
	Veraloc	tablets
	Veraloc Retard	prolonged-release tablets
	Verapamil ‘1A Farma’	prolonged-release tablets
	Verapamil ‘HEXAL’	prolonged-release tablets
	Verapamil ‘HEXAL’	film-coated tablets
	Verapamil ‘Merck NM’	film-coated tablets
C08DB01	Cardil	prolonged-release tablets
	Cardizem	film-coated tablets
	Cardizem Retard	prolonged-release tablets
	Cardizem Unotard	prolonged-release tablets
	Dilcor	prolonged-release capsules
	Dilcor Uno	prolonged-release capsules
	Myonil	film-coated tablets
	Myonil Retard	prolonged-release tablets
	Myonil Uno	prolonged-release tablets
	Tilker	prolonged-release capsules, hard

Appendix III/C08: Price and consumption list of calcium channel blockers, combination products

Average lowest unit price calculated over six price periods (for the period 22 September 2008 to 14 December 2008)

1. ATC	2. Active substance/group	3. Number of persons treated		4. Pharmaceutic. form	5. Strength (mg)	6. Avg. lowest unit price (DKK)
		2006	2007			
C08DA	**Phenylalkylamine deriv.**					
C08DA51	Verapamil and trandolapril	767	665	Tab. w/mod. release	180+2 / 240+4	7.06 9.36
	Verapamil			Prolonged-rel. tab.	180 / 240	2.64 0.87
	Verapamil			Prol.-rel. cap., hard	240	2.72
	Trandolapril			Capsules	2	0.67

Name and form of medicinal product

ATC	Name	Form
C08DA51	Tarka	tablets with modified release