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 C03

Decision on future reimbursement status for medicinal products in ATC group C03 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 C03 (diuretics).

The decision is an overall decision on the reimbursement status **as of 13 July 2009** for all medicinal products of all strengths (unless otherwise stated) in ATC group C03, 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.

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.

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

Decision

1. Oral medicinal products in ATC group C03 containing the individual substances

- bendroflumethiazide (C03AA01)
- indapamide (C03BA11)
- furosemide (C03CA01)
- bumetanide (C03CA02)
- spironolactone (C03DA01)

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[1].

2. Oral medicinal products in ATC group C03 containing the individual substance

- eplerenone (C03DA04)

maintain their current reimbursement status (no general reimbursement) as of 13 July 2009.

The Danish Medicines Agency finds that this medicinal product is comprised by the exception set out in section 1(3), item 2 of the executive order on reimbursement. In the opinion of the Danish Medicines Agency, there is an obvious risk that the medicinal product will be used outside the approved indication in cases where this is inappropriate. We do not find that any exceptional circumstances apply which could provide the basis for another result.

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 this medicinal product which independently meet the criteria set out in the executive order on reimbursement for being granted general reimbursement (general conditional reimbursement).

3. Oral combination products in ATC group C03 containing

- bendroflumethiazide and potassium (C03AB01)
- bumetanide and potassium (C03CB02)
- hydrochlorothiazide and amiloride (C03EA01)
- furosemide and amiloride (C03EB01)

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

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

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.

4. Injection fluids in ATC group C03 containing the individual substances

- furosemide (C03CA01)
- bumetanide (C03CA02)

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.

Grounds

In its recommendation of 29 January 2008, the Reimbursement Committee stated that, based on an overall assessment of the group of diuretics, their application areas, the number of patients treated with the individual substances as well as the price of treatment per day for the medicinal products, the Committee is of the opinion that the consumption is rational and that there is no basis for changing the reimbursement status for these medicinal products.

The Committee stated that the medicinal products should primarily be used for the treatment of hypertension, heart insufficiency and generalised oedema, and that the thiazides should be preferred to the other diuretics provided their effect is adequate.

The Reimbursement Committee emphasised that the price of treatment per day for oral treatment is in the lower end of the price scale for medicinal products for the treatment of hypertension, from DKK 0.23 to DKK 2.84 for individual substances and DKK 0.83 to DKK 3.33 for the combination products, and that the medicinal products can also be used for other indications than hypertension and have partially different mechanisms of action.

The Reimbursement Committee also emphasised that consumption data for 2006 showed that bendroflumethiazide with potassium and furosemide account for the majority of the consumption of diuretics and that the consumption of bumetanide is relatively low. The price of treatment per day for bendroflumethiazide and potassium was DKK 0.83 to DKK 1.40 and DKK 0.27 to DKK 0.76 for furosemide for the tablet and prolonged release form. Of the more than 550,000 persons being treated with a diuretic, approx. 318,000 persons were treated with the combination of bendroflumethiazide and potassium and approx. 170,000 persons with furosemide.

As for eplerenone, the Committee was of the opinion that there is still a risk that it will be used outside the approved indication, e.g. for patients with light heart insufficiency without recent AMI or, in general, for patients with more severe heart insufficiency. The price of treatment per day of DKK 21.35 is very high compared to other diuretics. In the opinion of the Committee, it was not possible to identify parts of the indication which independently meet the criteria for being granted general reimbursement.

As for the injection products furosemide and bumetanide, the Reimbursement Committee emphasised that the medicinal products are sometimes prescribed to patients in nursing homes who cannot ingest the substances orally. The price of treatment was DKK 2.44 for furosemide and DKK 12.76 for bumetanide.

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/C03 contains an updated price and consumption list for individual substances in ATC group C03 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/C03 contains an updated price and consumption list specifying the average lowest unit prices calculated over the same period for combination products in ATC group C03 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 – Oral treatment
The Danish Medicines Agency emphasises the Reimbursement Committee's viewpoints, grounds and conclusions set out in the

Committee's recommendation of 29 January 2008 in relation to medicinal products in ATC group C03, cf. also above.

The Danish Medicines Agency also emphasises that the price of treatment per day for all oral individual substances and combination products in C03, with the exception of medicinal products containing eplerenone, is still in the lower end of the price scale, between DKK 0.17 and DKK 3.29 for medicinal products for the treatment of hypertension.

We emphasise that consumption data reflect that the thiazides account for the majority of the consumption which, along with other antihypertensives, are recommended for first-line treatment of hypertension provided their effect is adequate. Consumption data also show that furosemide accounts for the majority of the consumption of loop diuretics which are recommended for first-line treatment of patients with heart insufficiency requiring a diuretic, and that the consumption of bumetanide is relatively small.

The price of treatment for eplerenone is now DKK 23.44. The Danish Medicines Agency shares the Reimbursement Committee's opinion that there is a risk of inappropriate use of eplerenone outside the approved indication and does not, against this background, find any basis for granting general conditional reimbursement for eplerenone.

Re 2 – Individual substances for injection
As for the injection products furosemide and bumetanide, the Danish Medicines Agency emphasises the Reimbursement Committee's opinion that the medicinal products are prescribed to patients in nursing homes who cannot ingest the medicinal product orally. The Danish Medicines Agency emphasises the small consumption of bumetanide injection fluid and finds that this product is only used when furosemide cannot be used.

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

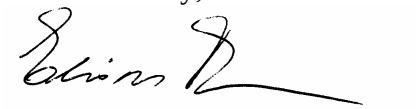
reimbursement status of all medicinal products should be reassessed regularly. The reimbursement status granted to the medicinal products following this decision will thus be reassessed in connection with this regular reassessment procedure.

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/C03: Price and consumption list of diuretics, 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)	7. Avg. lowest unit price(s) (DKK)	8. Avg. lowest price of treat. per day (DKK)
C03AA	**Thiazides, plain**	11,088	11,895					
C03AA01	Bendroflumethiazide	11,088	11,895	1.25 - 2.5 [2 5]	Tablets	5	0.89	0.22 - 0.45 [4]
C03BA	**Clopamide and indapamide**	6,510	6,096					
C03BA11	Indapamide	6,504	6,096	1.5 - 2.5 [2 6]	Prolonged-rel. tab.	1.5	1.85	1.85 - 3.08 [4]
	Indapamide	6,504	6,096	1.5 - 2.5 [2 6]	Film-coated tablets	2.5	1.67	1.00 - 1.67 [4]
C03CA	**Loop diuretics**	179,977	179,252					
C03CA01	Furosemide	176,796	176,240	40 [3]	Tablets	40	0.17	0.17
	Furosemide	176,796	176,240	40 [3]	Prolonged-rel. caps.	60 30	1.13 0.66	0.75 0.88 [4]
	Furosemide	176,796	176,240	40 [3]	Oral drops	10 mg/ml	0.72 DKK/ml	2.88
	Furosemide	176,796	176,240	40 [3]	Injection fluid	10 mg/ml	0.60 DKK/ml	2.40
C03CA02	Bumetanide	3,977	3,856	1 [3]	Tablets	1	2.49	2.49
	Bumetanide	3,977	3,856	1 [3]	Injection fluid	0.5 mg/ml	6.27 DKK/ml	12.54
C03DA	**Aldosterone antagonists**	46,049	46,463					
C03DA01	Spironolactone	45,710	46,021	25 - 100 [2 6]	Tablets	25 100	0.53 2.69	0.53 2.69
C03DA04	Eplerenone	481	576	50 [3]	Film-coated tablets	50	23.44	23.44

Notes/explanations:

1	Unless otherwise stated, the dose can be given once a day
2	Equieffective dose from IRF's background note
3	DDD value (WHO)
4	The medicinal product is not available in a strength that corresponds to the equieffective dose/the proposed dose
5	Recommended by IRF
6	Recommended by IRF with provisos or in special cases

Name and form of medicinal product

ATC	Name	Form
C03AA01	Centyl	tablets
C03BA11	Indacar	coated tablets
	Indapamide ‘Orifarm’	film-coated prolonged-release tablets
	Indapamide ‘Stada’	prolonged-release tablets
	Indapamide ‘Merck NM’	film-coated tablets
	Natrilix Retard	prolonged-release tablets
	Tertensif Retard	prolonged-release tablets
C03CA01	Diural	injection fluid, solution
	Diural	oral drops
	Diural	tablets
	Furese	tablets
	Furix	injection fluid, solution
	Furix	tablets
	Furix Retard	prolonged-release capsules, hard
	Furosemide ‘1A Farma’	tablets
	Furosemide ‘Copyfarm’	tablets
	Furosemide ‘DAK’	tablets
	Furosemide ‘HEXAL’	tablets
	Lasix	tablets
	Lasix Retard	prolonged-release capsules
C03CA02	Bumetanide ‘Copyfarm’	tablets
	Burinex	injection fluid, solution
	Burinex	tablets
C03DA01	Hexalacton	tablets
	Spirix	tablets
	Spiron	tablets
C03DA04	Inspra	film-coated tablets

Appendix III/C03: Price and consumption list of diuretics, 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			
C03AB	**Thiazides and potassium in combination**	317,663	318,155			
C03AB01	Bendroflumethiazide and potassium	317,663	318,155	Coated tab.	1,25+573 / 2,5+573	0.81 / 1.38
	Bendroflumethiazide			Tablets	5	0.89
	Potassium			Prolonged-rel. tab.	750	0.83
C03CB	**Loop diuretics and potassium in comb.**	3,232	3,102			
C03CB02	Bumetanide and potassium	3,232	3,102	Coated tablets	0,5+573	0.95
	Bumetanide			Tablets	1	2.49
	Potassium			Prolonged-rel. tab.	750	0.83
C03EA	**Low-ceiling diuretics and potassium-sp.**	28,980	27,629			
C03EA01	Hydrochlorothiazide and amiloride	28,980	27,629	Tablets	25+2,5 / 50+5	2.32 / 1.03
	Hydrochlorothiazide	---------- Not marketed in Denmark ----------				
	Amiloride	---------- Not marketed in Denmark ----------				
C03EB	**High-ceiling diuretics and potassium-sp.**	2,449	2,040			
C03EB01	Furosemide and amiloride	2,139	2,040	Film-coated tablets	40+5	3.29
	Furosemide			Tablets	40	0.17
	Amiloride	---------- Not marketed in Denmark ----------				

Name and form of medicinal product

ATC	Name	Form
C03AB01	Centyl with potassium chloride	coated tablets
C03AB01	Centyl Mite with potassium chloride	coated tablets
C03CB02	Burinex with potassium chloride	coated tablets
C03EA01	Amilco	tablets
	Sparkal	tablets
	Sparkal Mite	tablets
C03EB01	Frusamil	film-coated tablets