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 C07

Decision on future reimbursement status for medicinal products in ATC group C07 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 C07 (beta blocking agents).

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 C07, 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 2008 and 9 September 2008.

The recommendations of the Reimbursement Committee have been submitted to the affected companies, scientific societies, patient organisations etc. for consultation. In addition, we have carried out a consultation with updated prices for combination products containing metoprolol and felodipine (C07FB02).

Please see the consultation memorandum of today 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 C07 containing the individual substances

- pindolol (C07AA03)
- propranolol (C07AA05)
- sotalol (C07AA07)
- metoprolol (C07AB02)
- atenolol (C07AB03)
- acebutolol (C07AB04)
- bisoprolol (C07AB07)
- nebivolol (C07AB12)
- labetalol (C07AG01)
- carvedilol (C07AG02)

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 combination products in ATC group C07 containing

- metoprolol og hydrochlorothiazide (C07BB02)
- atenolol and chlorothalidone (C07CB03)

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.

3. Oral combination products in ATC group C07 containing

- metoprolol and felodipine (C07FB02)

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 this medicinal product which independently meet the criteria set out in the executive order on

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

reimbursement for being granted general reimbursement (general conditional reimbursement).

4. Injection products in ATC group C07 containing
- sotalol (C07AA07)
- metoprolol (C07AB02)
- esmolol (C07AB09)
- labetalol (C07AG01)

maintain their reimbursement 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 of the characteristics of the oral beta blocking agents, their application areas, the number of patients treated with the individual active 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 recommended that, in future, medicinal products for injection containing the active substances sotalol, metoprolol and labetolol should not be granted general reimbursement as these medicinal products, in the opinion of the Committee, are exclusively used in hospitals or, e.g., within the emergency service.

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/C07 contains an updated price and consumption list for individual substances in ATC group C07 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/C07 contains an updated price and consumption list specifying the average lowest unit prices calculated over the same period for combination products in ATC group C07 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 – Individual substances for oral treatment
The Danish Medicines Agency emphasises what the Reimbursement Committee stated in relation to oral individual substances in ATC group C07 in the Committee's recommendation of 29 January 2008.

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 C07 was between DKK 0.23 and DKK 6.04 stated at reimbursement prices. The price of treatment per day for labetolol, which is used for the treatment of hypertension in pregnant women, was somewhat higher, between DKK 3.19 and DKK 11.52.

The price of treatment for oral treatment with the individual substances in ATC group C07 (with the exception of labetolol) have not changed significantly and are now between DKK 0.23 and DKK 6.80 stated at reimbursement prices.

The price of treatment per day for labetolol is at the same level as the price of treatment at the time of the Committee's decision.

Re 2 and 3 – Combination products for oral treatment
As the basis of our assessment of the future reimbursement status for combination products in ATC group C07, 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/C07**.

This information shows that the price of the combination product containing metoprolol and felodipine is DKK 6.24 which is significantly more than the price of the individual substances. Metoprolol costs DKK 1.53 to DKK 1.65 and felodipine costs DKK 0.45.

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 metoprolol and felodipine 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.

For combination products containing metoprolol and hydrochlorothiazide as well as atenolol and chlorothalidone, the Danish Medicines Agency finds that the relationship between the price of the medicinal products and their therapeutic value is reasonable when compared with the prices of the individual substances marketed in separate formulations. Furthermore, the prices are in the lower end of the price scale for oral treatment of hypertension requiring treatment.

The consumption is at the same level as the consumption on which the Committee based its recommendation of 29 January 2008 and does not give rise to any comments.

Re 4 – Injection products
The Danish Medicines Agency emphasises what the Reimbursement Committee stated in relation to injection products in ATC group C07 in the Committee's recommendation of 29 January 2008, viz. that these medicinal products are exclusively used in hospitals and should thus 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).

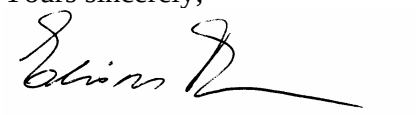
Reassessment
In connection with the introduction of the reassessment of the reimbursement status of medicinal products in 2005, it was decided that the reimbursement status of all medicinal products should be reassessed regularly. The reimbursement status granted to the medicinal products following this 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/C07: Price and consumption list of beta blocking agents, 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)
C07AA	**Beta blocking agents, plain, non-selective**	46,693	44,247					
C07AA03	Pindolol	2,748	2,422	10 - 15 [3 5]	Tablets	10 / 15	2.44 / 2.93	2.44 - 2.93
C07AA05	Propranolol	36,598	35,736	80 - 320 [2 3 5]	Film-coated tab./tab.	40 / 80	0.25 / 0.36	0.50 - 1.44
	Propranolol	36,598	35,736	80 - 320 [3 5]	Prol.-rel. caps, hard	80 / 160	2.32 / 3.40	2.32 - 6.80
C07AA07	Sotalol	7,403	6,144	160 [2 4 7]	Tablets	80	1.07	2.14
	Sotalol	7,403	6,144	160 [2 4 7]	Injection fluid	10 mg/ml	Approved, but no longer marketed	
C07AB	**Beta blocking agents, plain, selective**	261,821	272,252					
C07AB02	Metoprolol	201,512	213,447	50 - 200 [3 5]	Tablets	50 / 100	0.98 / 1.09	0.98 - 2.18
	Metoprolol	201,512	213,447	50 - 200 [3 5]	Prolonged-rel. tab	50 / 200	1.53 / 3.72	1.53 - 3.72
	Metoprolol	201,512	213,447	50 - 200 [3 5]	Prolonged-rel. tab	50 / 200	1.63 3.50	1.63 - 3.50
	Metoprolol	201,512	213,447	150 [4]	Injection fluid	1 mg/ml	5.13	769.50
C07AB03	Atenolol	41,793	38,982	50 - 100 [3 5]	Film-coated tablets	50 / 100	0.23 / 0.45	0.23 - 0.45
C07AB04	Acebutolol	443	411	200 - 400 [3 5]	Tablets	200 / 400	3.14 / 5.97	3.14 - 5.97
C07AB07	Bisoprolol	20,261	21,490	5 - 10 [3 5]	Film-coated tablets	5 / 10	1.23 / 1.09	1.23 - 1.09
C07AB09	Esmolol			2.5 [4]	Injection fluid	10 mg/ml	10.47	2.62
C07AB12	Nebivolol		114	5 [4]	Tablets	5	4.62	4.62
C07AG	**Alpha and beta blocking agents**	25,523	27,339					
C07AG01	Labetalol	2,251	2,331	300 - 1200 [3 6 9]	Film-coated tablets	100 / 200	1.25 / 1.89	3.14 - 11.34
	Labetalol	2,251	2,331	600 [4]	Injection fluid	5 mg/ml	5.06	607.20
C07AG02	Carvedilol	23,330	25,049	25 [3 5]	Film-coated tab./tab.	25	0.52	0.52

Notes/explanations:

1	Unless otherwise stated, the dose can be given once a day
2	Divided into two doses
3	Proposed dose from IRF's background note
4	DDD value (WHO)
5	Recommended by IRF
6	Recommended by IRF with provisos or in special cases
7	Not recommended by IRF
8	The medicinal product is not available in a strength that corresponds to the equieffective dose/the proposed dose
9	Divided into 2-6 daily doses

Name and form of medicinal product

ATC	Name	Form
C07AA03	Hexapindol	tablets
	Pindolol ‘Mylan’	tablets
	Visken	tablets
C07AA05	Propal Retard	prolonged-release capsules, hard
	Propranolol ‘DAK’	film-coated tablets
	Propranolol ‘Merck NM’	film-coated tablets
C07AA07	Sotacor	injection fluid
	Sotalol ‘Actavis’	tablets
	Sotalol ‘Merck NM’	tablets
C07AB02	Betaloc ZOK	prolonged-release tablets
	Mepronet	tablets
	Metocar	tablets
	Metoprolol ‘1A Farma’	prolonged-release tablets
	Metoprolol ‘GEA’	prolonged-release tablets
	Metoprololsuccinate ‘1A Farma’	prolonged-release tablets
	Metoprololsuccinate ‘Hexal’	prolonged-release tablets
	Metoratio	prolonged-release tablets
	Seloken	injection fluid, solution
	Selo-zok	prolonged-release tablets
C07AB03	Atenet	tablets
	Atenodan	tablets

	Atenolol ‘Merck NM’	film-coated tablets
	Atenolol ‘Orifarm’	tablets
	Atenolol ‘Sandoz’	tablets
	Atenor	film-coated tablets
	Tenormin	film-coated tablets
	Uniloc	tablets
C07AB04	Diasectral	tablets
C07AB07	Bisocor	film-coated tablets
	Bisoprolol ‘Alpharma’	tablets
	Bisoprolol ‘Sandoz’	film-coated tablets
	Bisoprolol ‘Stada’	film-coated tablets
	Cardicor	film-coated tablets
	Emconcor	film-coated tablets
C07AB09	Brevibloc	injection fluid, solution
C07AB12	Hypoloc	tablets
C07AG01	Trandate	film-coated tablets
	Trandate	injection fluid, solution
C07AG02	Carvedilol ‘Alternova’	tablets
	Carvedilol ‘HEXAL’	tablets
	Carvedilol ‘KRKA’	tablets
	Carvedilol ‘Orion Pharma’	film-coated tablets
	Carvedilol ‘PCD’	tablets
	Carvedilol ‘ratiopharm’	tablets
	Carvedilol ‘Sandoz’	tablets
	Carvedilol ‘Teva’	tablets
	Carvedilol ‘UNP’	film-coated tablets
	Dimitone	tablets

Appendix III/C07: Price and consumption list of beta blocking agents, 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			
C07BB	**Beta blocking agents, selective, and thiazides**	2,767	2,703			
C07BB02	Metoprolol and hydrochlorothiazide	2,767	2,703	Prolonged-rel. tab.	100+12,5	3.72
	Metoprolol			Prolonged-rel. tab.	100 / 100 [1]	2.20 3.01
	Hydrochlorothiazide	---------- Not marketed in Denmark ----------				
C07CB	**Beta block. agents, selective, and other diuretics**	4,278	3,941			
C07CB03	Atenolol and Chlorothalidone	4,278	3,941	Film-coated tablets	50+12,5 / 100+25	1.23 / 2.90
	Atenolol			Film-coated tablets	50 / 100	0.23 0.49
	Chlorothalidone	---------- Not marketed in Denmark ----------				
C07FB	**Beta block. agents, selective, and other antihyp.**	1,252	1,208			
C07FB02	Metoprolol and felodipine	1,252	1,208	Prolonged-rel. tab.	50+5	6.24
	Metoprolol			Prolonged-rel. tab.	50 / 50 [1]	1.53 1.65
	Felodipine			Prolonged-rel. tab.	5	0.45

Notes/explanations:

1	Two different substitution groups

Name and form of medicinal product

ATC	Name	Form
C07BB02	Zok-Zid	prolonged-release tablets
C07CB03	Tenidon	film-coated tablets
	Tenidon Mite	film-coated tablets
	Tenoretic	film-coated tablets
	Tenoretic Mite	film-coated tablets
C07FB02	Logimax	prolonged-release tablets