LÆGEMIDDEL STYRELSEN
DANISH MEDICINES AGENCY

For companies which, as of 31 May 2010 or before,
have marketed one or more medicinal products in ATC group A02

Decision on future reimbursement status of medicinal products in ATC group A02

11 June 2010

Case no.:
5315-5

This decision concludes the Danish Medicines Agency's reassessment of the reimbursement status of medicinal products in ATC group A02, drugs for acid-related disorders.

The decision is an overall decision on the reimbursement status **as of 15 November 2010** for all medicinal products[1] in ATC group A02 which are approved for marketing in Denmark and which are or have been marketed as of 31 May 2010.

Presentation
On 10 December 2009, 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 reassessment process. The Committee's recommendation is available at
http://www.dkma.dk/1024//visUKLSSArtikel.asp?artikelID=15937.

The Committee's recommendation has been submitted to the concerned companies and relevant scientific societies for consultation. Seven consultation responses were received, which are available (in Danish) at
http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=16338

All consultation responses were presented to the Committee at a meeting held on 23 March 2010. The Committee maintained its recommendation of 10 December 2009.

[1]Medicinal products with a magnesium hydroxide content (A02AA04) have not been included, as the reimbursement status of these medicinal products have previously been reassessed together with medicinal products in ATC group A06, laxatives.

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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 prices of treatment on which the decision is based are the same that formed the basis of the Committee's recommendation of 10 December 2009 and appear from Appendix B to the Committee's recommendation. The 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.

The calculations are based on equieffective doses when such doses have been assigned, alternatively on DDD values assigned by the WHO or on the doses indicated at Medicin.dk. The period applied covers the six price periods, the first period beginning on 21 September 2009 and the last period beginning on 30 November 2009.

In support of this decision, the Agency has prepared a new price survey (Appendix 2) containing the prices of the Committee's Appendix B as well as updated prices based on six price periods, the first period beginning on 8 March 2010 and the last period beginning on 17 May 2010. The statement below that prices have not changed considerably in relation to the prices on which the Committee's recommendation of 10 December 2009 was based is made with reference to the updated prices in Appendix 2.

A number of the medicinal products involved may be sold outside pharmacies at prices determined locally by the sales outlet. There is no obligation to report such prices to the Agency. For these non-pharmacy-restricted medicinal products, the prices of treatment on which the Committee's decision is based are calculated on the basis of the prices reported by the sales outlets to the Register of Medicinal Product Statistics at the Danish Medicines Agency for the period between 3 August 2009 and 25 October 2009 (the latest validated figures preceding the Committee's recommendation, corresponding to six price periods).

In support of this decision, the Agency has also updated these prices in Appendix 2. The prices stated in Appendix 2 have been calculated on the basis of the prices which the sales outlets have reported to the Register of Medicinal Product Statistics at the Danish Medicines Agency for the period between 28 December 2009 and 21 March 2010 (the latest validated figures, corresponding to six price periods).

Cimetidine was taken off the market on 25 February 2008, and the prices on which the Committee's recommendation and the Agency's decision on

this medicinal product are based are from the period between 3 December 2007 and 24 February 2008.

We do not find that the updated prices give rise to another assessment than the one stated below.

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

Decision

1.
All medicinal products in ATC group A02AB (aluminium compounds) containing the individual substance:

- Dihydroxyaluminium sodium carbonate (A02AB04)

maintain their current reimbursement status – no general reimbursement.

With reference to section 144(3) of the Danish Health Act, the Danish Medicines 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[2] for being granted general reimbursement (general conditional reimbursement), cf. section 1(2) of the executive order.

2.
All medicinal products in ATC group A02AD (combinations and complexes of aluminium, calcium and magnesium compounds) containing the combinations:

- Anhydrous aluminium aminoacetate and magnesium oxide (A02AD01)
- Calcium carbonate and magnesium hydroxide (A02AD01)
- Aluminium hydroxide/magnesium carbonate co-precipitate (A02AD01)
- Aluminium oxide and magnesium oxide (A02AD01)

maintain their current reimbursement status – no general reimbursement.

With reference to section 144(3) 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

[2]Danish executive order no. 180 of 17 March 2005 on medicine reimbursement

reimbursement (general conditional reimbursement), cf. section 1(2) of the executive order.

3.
Oral medicinal products in ATC group A02BA (H2 receptor antagonists) containing the individual substances:

- Cimetidine (A02BA01)
- Ranitidine (A02BA02)

will have their reimbursement status changed from general conditional reimbursement to no general reimbursement.

The conditions being removed are:

> Cimetidine:
> "Ulcus duodeni. Ulcus ventriculi. Reflux oesophagitis. Zollinger-Ellison syndrome."
>
> Ranitidine:
> "Ulcus duodeni. Ulcus ventriculi. Reflux oesophagitis. Zollinger-Ellison syndrome. Gastroscopically verified Helicobacter pylori-associated ulcus in combination with antibiotics."

With reference to section 144(3) 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.

- Nizatidine (A02BA04)

will have its reimbursement status changed from general 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 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.

4.
All medicinal products in ATC group A02BB (prostaglandins) containing the individual substance:

- Misoprostol (A02BB01)

will have their reimbursement status changed from general 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 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.

5.
Oral medicinal products in ATC group A02BC (proton pump inhibitors) containing the individual substances:

- Omeprazole (A02BC01), enteric-coated tablets and enteric-coated capsules 10 mg in packages up to and including 56 pcs.[3]
- Pantoprazole (A02BC02), enteric-coated tablets 20 mg in packages up to and including 28 pcs.[4]
- Lansoprazole (A02BC03), enteric-coated capsules 15 mg in packages up to and including 56 pcs.[5]

maintain their current reimbursement status – general conditional reimbursement.

The reimbursement condition for omeprazole will be changed from:

> "Ulcus duodeni. Ulcus ventriculi. Reflux oesophagitis. Zollinger-Ellison syndrome." to
>
> "Symptomatic gastroesophageal reflux disease."

to make the condition comply with the approved indication.

[3]Over the counter
[4]Over the counter
[5]Over the counter

The reimbursement condition for lansoprazole will be changed from:

> "Ulcus duodeni. Ulcus ventriculi. Reflux oesophagitis. Zollinger-Ellison syndrome. Gastroscopically verified Helicobacter pylori-associated ulcus in combination with antibiotics." to:
>
> "Symptomatic gastroesophageal reflux disease."

to make the condition comply with the approved indication.

The reimbursement condition for pantoprazole is still:

> "Reflux symptoms"

With reference to section 144(3) of the Danish Health Act, the Danish Medicines Agency finds that these medicinal products, when used as stated in the condition, *meet* the criteria for being granted general reimbursement (general conditional reimbursement), cf. section 1(2) of the executive order on reimbursement.

6.
Oral medicinal products in ATC group A02BC (proton pump inhibitors) containing the individual substances:

- Omeprazole (A02BC01), all other strengths and packages that those mentioned under item 5 above
- Pantoprazole (A02BC01), all other strengths and packages that those mentioned under item 5 above
- Lansoprazole (A02BC01), all other strengths and packages that those mentioned under item 5 above

maintain their current reimbursement status – general reimbursement.

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.

7.
Oral medicinal products in ATC group A02BC (proton pump inhibitors) containing the individual substances:

- Rabeprazole (A02BC04)
- Esomeprazole (A02BC05)

will have their reimbursement status changed from general 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 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.

8.
Oral medicinal products in ATC group A02BX (other products against ulcer and gastroesophageal reflux (GERD)) containing the individual substance:

- Sucralfate (A02BX02)

will have its reimbursement status changed from general conditional reimbursement to no general reimbursement.

The condition being removed is:

"Ulcus ventriculi. Reflux oesophagitis."

With reference to section 144(3) 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.

9.
Oral medicinal products in ATC group A02BX (other products against ulcer and gastroesophageal reflux (GERD)) containing the individual substance:

- Alginic acid (A02BX13)

maintain their current reimbursement status – no general reimbursement.

With reference to section 144(3) 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.

10.
All medicinal products **for injection/infusion** in ATC group A02 containing the individual substances:

- Ranitidine (A02BA02)
- Omeprazole (A02BC01)
- Pantoprazole (A02BC02)
- Esomeprazole (A02BC05)

maintain their current reimbursement status – no general reimbursement.

These medicinal products *do not meet* the criteria for being granted general reimbursement, cf. section 1(3)(viii) and (ix) of the executive order on reimbursement. We do not find that any exceptional circumstances apply in this case which may lead to a different outcome.

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.

Grounds
The Danish Medicines Agency generally emphasises that in its recommendation of 10 December 2009, the Reimbursement Committee refers to the fact that the proton pump inhibitors are generally first-line treatment for all conditions in which medicinal products for the treatment of acid-related disorders are indicated.

Re 1. and 2. – Antacids
With reference to the fact that antacids have poorer effect and higher dosage frequency than the proton pump inhibitors, the Reimbursement Committee states in its recommendation of 10 December 2009 that the Committee does not find that the relationship between therapeutic value of these medicinal products and the prices of between DKK 0.58 and 3.40 per dose is reasonable when compared with the therapeutic value of medicinal products containing omeprazole, lansoprazole and pantoprazole.

We emphasise the recommendation of the Reimbursement Committee and do not find that the relationship between the price of antacids and their therapeutic value is reasonable. Therefore, these medicinal products will continue to be non-eligible for general reimbursement.

Re 3. – H2 receptor antagonists

With reference to the fact that these medicinal products have poorer effect than the proton pump inhibitors and that cimetidine has more drug interactions than the proton pump inhibitors, and with reference to the fact that the prices of treatment of these medicinal products are between DKK 4.26 and 6.90 per day[6], the Reimbursement Committee states in its recommendation of 10 December 2009 that the Committee does not find that the relationship between the prices of H2 receptor antagonists and their therapeutic value is reasonable when compared with the therapeutic value of medicinal products containing omeprazole, lansoprazole and pantoprazole, costing between DKK 0.65 and 0.91 per day in equieffective doses, cf. Appendix B.

We emphasise the recommendation of the Reimbursement Committee and do not find that the relationship between the price of H2 receptor antagonists and their therapeutic value is reasonable, and we find that these medicinal products should no longer be eligible for general reimbursement and general conditional reimbursement, respectively.

Re 4. – Misoprostol
In its recommendation of 10 December 2009, the Reimbursement Committee states that misoprostol is just as effective as proton pump inhibitors in preventing ASA/NSAID-related ulcus, but that it is not recommended due to the adverse reactions of the medicinal product. In reference hereto, the Committee does not find that the relationship between the the price of DKK 13.68 per day and the therapeutic value is reasonable when compared with the proton pump inhibitors omeprazole, lansoprazole and pantoprazole, which cost between DKK 0.65 and 0.91 per day in equieffective doses, cf. Appendix B.

We emphasise the recommendation of the Reimbursement Committee and do not find that the relationship between the price of misoprostol and its therapeutic value is reasonable, and we find that these medicinal products should no longer be eligible for general reimbursement.

Re 5. – Proton pump inhibitors: omeprazole, lansoprazole and pantoprazole – over the counter
With reference to the Reimbursement Committee, in its recommendation of 10 December 2009, referring to the fact that proton pump inhibitors are generally first-line treatment for all conditions in which medicinal products for the treatment of acid-related disorders are indicated, and that a class effect exists between the proton pump inhibitors, the Danish Medicines Agency finds that the relationship between the therapeutic value of these medicinal products, costing between DKK 0.80 and 1.79 per day in equieffective doses when used as indicated in the condition, and the price of said medicinal products is reasonable.

[6]Medicinal products containing cimetidine have not been marketed since February 2008. At that time, the price of treatment per day for cimetidine was DKK 1.98-2.07.

Against this background, these medicinal products maintain general conditional reimbursement.

Re 6. – Proton pump inhibitors: omeprazole, lansoprazole and pantoprazole – prescription

With reference to the Reimbursement Committee, in its recommendation of 10 December 2009, referring to the fact that proton pump inhibitors are generally the first-line treatment for all conditions in which medicinal products for the treatment of acid-related disorders are indicated, and that a class effect exists between the proton pump inhibitors, the Danish Medicines Agency finds that the relationship between the therapeutic value of these medicinal products, costing between DKK 0.65 and 0.91 per day in equieffective doses, and the price of said medicinal products is reasonable.

Against this background, these medicinal products maintain general reimbursement.

Re 7. – Proton pump inhibitors: rabeprazole and esomeprazole

With reference to the fact that a class effect exists between the proton pump inhibitors, that no clinically relevant differences have been documented for the individual proton pump inhibitors in equieffective doses and that the average lowest prices of treatment per day are DKK 10.71 for rabeprazole and DKK 5.37 for esomeprazole in the form of tablets and DKK 24.04 for esomeprazole in the form of enteric-coated granulate, the Reimbursement Committee assesses, in its recommendation of 10 December 2009, that the relationship between the prices of these medicinal products and their therapeutic value is not reasonable when compared with the average lowest prices of treatment per day for medicinal products containing the other proton pump inhibitors omeprazole, pantoprazole and lansoprazole, which in the equieffective doses of the tablet forms cost between DKK 0.65 and 0:91 per day.

We emphasise the recommendation of the Reimbursement Committee and do not find that the relationship between the price of these medicinal products and their therapeutic value is reasonable, and we find that these medicinal products should no longer be eligible for general reimbursement. The fact that the price of esomeprazole has increased and the price of rabeprazole has decreased, cf. Appendix 2 (period 2), after the Reimbursement Committee having submitted its recommendation on 10 December 2009 does not change our assessment.

In its consultation response of 12 March 2010, AstraZeneca suggests that esomeprazole become eligible for general conditional reimbursement for "patients with verified oesophagitis and patients requiring treatment with antacids who have not yet achieved sufficient effect through treatment with products eligible for general reimbursement."

Since esomeprazole, with reference to the class effect, is only to be used in the few cases where treatment with proton pump inhibitors eligible for general reimbursement has been found to be insufficient, the Danish Medicines Agency finds that the number of patients with a specific need for treatment with esomeprazole is small. In the Agency's view, general conditional reimbursement as suggested will entail a risk of esomeprazole being used as first-line treatment in cases where the Agency does not consider this to be reasonable. With reference to section 1(3), item 5 of the executive order on reimbursement, the Danish Medicines Agency does not find that the criteria for general conditional reimbursement targeted at patients covered by the suggested condition meets the criteria of the executive order on reimbursement for being eligible for general (conditional) reimbursement. We do not find that any exceptional circumstances apply which may justify a different outcome.

Re 8. – Sucralfate
With reference to the fact that sucralfate is less effective than the proton pump inhibitors, that the active substance must be dosed four times per day and that drug interaction exists with other medicinal products for the treatment of similar indications, the Reimbursement Committee states in its recommendation of 10 December 2009, with reference to the average lowest price of treatment per day being DKK 10.28, that the relationship between the price of treatment of sucralfate and its therapeutic value is not reasonable when compared with the proton pump inhibitors omeprazole, lansoprazole and pantoprazole, costing between DKK 0.65 and 0.91 per day for an equieffective dose, cf. Appendix B.

We emphasise the recommendation of the Reimbursement Committee and do not find that the relationship between the price of sucralfate and its therapeutic value is reasonable, and we find that these medicinal products should no longer be eligible for general conditional reimbursement.

Re 9. – Alginic acid
With reference to the fact that alginic acid is less effective than the proton pump inhibitors and is not recommended, the Reimbursement Committee does not find in its recommendation of 10 December 2009, with reference to the fact that the lowest price of the smallest single dose is DKK 1.41, that the relationship betwween the price of treatment of alginic acid and its therapeutic value is reasonable when compared with the proton pump inhibitors omeprazole, lansoprazole and pantoprazole, costing between DKK 0.65 and 0.91 per day for an equieffective dose, cf. Appendix B.

We emphasise the recommendation of the Reimbursement Committee and do not find that the relationship between the price of alginic acid and its therapeutic value is reasonable, and we find that these medicinal products should continue to be non-eligible for general reimbursement.

Re 10. – Medicinal products for injection/infusion in A02
With reference to the fact that the H2 receptor antagonist ranitidine and the proton-pump inhibitors omeprazole, pantoprazole and esomeprazole in pharmaceutical forms intended for injection and infusion are primarily used in hospitals and cannot be ingested by the patients themselves, the Reimbursement Committee states in its recommendation of 10 December 2009 that these medicinal products should continue to be non-eligible for general or general conditional reimbursement.

We concur with the Reimbursement Committee's recommendation and find that these medicinal products still do not comply with the Committee's criteria for 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 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.

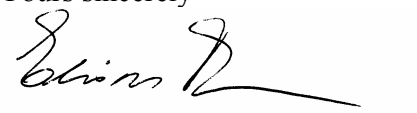
In addition, the Danish Medicines Agency can initiate ad hoc reassessments, e.g. when we receive important new information about inappropriate consumption, new treatment recommendations, significant price changes etc. The Agency monitors the development in the consumption and prices of medicinal products 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 Danish Medicines 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 ulcers in ATC group A02
Appendix 2: Price survey

Danish Medicines Agency
Case no. 5315-5
11 June 2010

Appendix 1 – Note on consultation on proposals for future reimbursement status of medicinal products for ulcers in ATC group A02

1. Parties to the consultation

Concerned companies:
1A Farma A/S, 2care4 ApS, A Generic Pharmaceutical AB, Actavis Group, Actavis Group hf., Actavis Nordic A/S, Arrow Generics Limited, AstraZeneca A/S, BioPhausia AB, Bluefish Pharmaceuticals AB, BMM Pharma AB, Copyfarm A/S, Eisai AB, EuroPharmaDK ApS, GlaxoSmithKline Pharma A/S, HEXAL A/S, Krka Sverige AB, Mylan AB, Nordic Drugs AB, Nycomed Danmark ApS, Nycomed GmbH, OBA - Pharma ApS, Orifarm A/S, Orifarm Generics A/S, Orion Corporation, Orion Pharma, Paranova Danmark A/S, Pfizer ApS
PharmaCoDane ApS, Ranbaxy (UK) Ltd., ratiopharm GmbH, Recept Pharma AB, Sandoz A/S, Sandoz GmbH, Singad Pharma ApS, Stada Arzneimittel AG, Teva Denmark A/S

Medical scientific societies:
Danish Endocrine Society, Danish Society for Gastroenterology, Danish Gerontological Society, Danish Surgical Society, Danish Medical Society, Danish Paediatric Society, Danish College of General Practitioners, Danish Society of Geriatrics, Danish Association for the Study of the Liver, Danish Society of Internal Medicine, Danish Society for Clinical Nutrition and Metabolism, Danish Society of Clinical Pharmacology and Danish Society of Clinical Oncology.

Patient organisations:
Danish Patients, Disabled Peoples Organisations Denmark.

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

The Danish Medicines Agency has received seven consultation responses. A link to the responses can be found here:
http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=16338

We presented all the responses to the Reimbursement Committee, requesting the Committee's comments on the medical and pharmaceutical is-

sues. The responses were discussed at the Committee's meeting on 23 March 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.

AstraZeneca claims that the Reimbursement Committee's recommendation is based on an incomplete and undocumented basis and claims that the Reimbursement Committee has not taken appropriate consideration of the fact that proton pump inhibitors are primarily to be used for the treatment of reflux disease, and that differentiation needs to be made within the group of patients with actual reflux disease. AstraZeneca believes that this simplification has entailed an unsubtle conclusion and that the Reimbursement Committee has not presented facts to substantiate the assumption that largely everybody can be treated with omeprazole, lansoprazole or pantoprazole.

We disagree in this matter. The Reimbursement Committee's recommendation of 10 December 2009 is based on the National Recommendation List, Recommendation and background note on products for acid-related disorders (A02), revised 10 February 2009, and the Danish College of General Practitioners' clinical guideline on dyspepsia and the assessment and treatment of adults with symptoms from stomach and intestines from 2009, which sources are evidence-based and concur in their conclusion that clinical endpoint studies do not indicate considerable difference between the different proton pump inhibitors used in equieffective doses.

The National Recommendation List mentions that esomeprazole 40 mg has been shown to be marginally more effective than 20 mg as regards ulcer healing and pain relief (primarily at Los Angeles levels C and D), but no further questions are raised as to the proton pump inhibitors being equal. However, no comparisons exist between esomeprazole 40 mg and proton pump inhibitor regimens in which the dose is equieffective. In the few cases where it turns out that the standard proton pump treatment is not sufficient, it will be possible for the doctor to apply for single reimbursement for e.g. esomeprazole.

Among other things, AstraZeneca argues that the references to the Danish College of General Practitioners' guideline on dyspepsia are taken out of context, as the item 'Choice of antacid treatment', under which it is stated that no clinically relevant differences have been documented for the individual types of proton pump inhibitors in equipotent doses, in the view of AstraZeneca only refers to the item 'Assessment and treatment of gastroesophageal reflux'.

We disagree in this matter. The item 'Choice of antacid treatment' is equal to the other items and forms the conclusion of the guideline as regards choice of antacid treatment within dyspepsia in general. One of the central conclusions of the guideline is that the proton pump inhibitors are equal.

AstraZeneca claims that the Reimbursement Committee has not stated on which facts the conclusion on price in relation to therapeutic value is based.

The prices of treatment per day forming the basis of the recommendation are calculated in accordance with the Danish Medicines Agency's guidelines for evaluation and comparison of medicinal products in reassessments of reimbursement status dated 4 July 2006. The calculations are based on equieffective doses when such doses have been assigned, alternatively on DDD values assigned by the WHO or on the doses indicated at Medicin.dk. As regards the proton pump inhibitors, the Reimbursement Committee, in its recommendation of 10 December 2009, makes reference to the equieffective doses for the indication 'ulcer healing' stated in the National Recommendation List and notes that the equieffective doses for the other indications are either the same or half (for eradication treatment the double, however). As regards facts concerning the therapeutic value of the medicinal products, we refer to our comments above.

AstraZeneca criticises the Reimbursement Committee's recommendation for not containing an estimate of which patients may benefit especially from esomeprazole and makes reference to experience from Sweden, Canada, the USA and Norway which shows that the share of patients who do not achieve satisfactory treatment with generics is 10-20%, corresponding to approx. 60,000 people (2008 figures). It is also criticised that the Committee refers to consumption figures for 2008.

It is correct that the Reimbursement Committee's recommendation of 10 December 2009 does not contain an estimate of which patients could benefit especially from esomeprazole. The Committee says: "There is reason to assume that largely everybody can be treated with omeprazole, lansoprazole or pantoprazole, which are recommended to maintain general reimbursement." With reference to the fact that the share of patients who were prescribed esomeprazole and rabeprazole in 2008 was around 30% of all patients being treated with proton pump inhibitors prescribed by a doctor, the Committee states that it does not find the consumption to be rational.

The consumption figures for 2009, which are now available at http://www.medstat.dk/, indicate that approx. 105,000 people or almost 24% of all patients being treated with proton pump inhibitors prescribed by a doctor are being treated with esomeprazole and rabeprazole. The figures also show that this 24% share of the patients represents almost 64% of the sale of proton pump inhibitors.

The Danish Medicines Agency places emphasis on the Reimbursement Committee's reference to the fact that clinical endpoint studies do not show considerable difference between the different proton pump inhibitors used in equieffective doses and the Committee's assessment that there will only be few cases in which a patient may be in need of esomeprazole or rabeprazole, and the Agency assesses against this background that the consumption of these active substances is still not rational.

AstraZeneca suggests that esomeprazole become eligible for general conditional reimbursement for patients with verified oesophagitis and patients requiring treatment with antacids who have not yet achieved sufficient effect through treatment with products eligible for general reimbursement.

We refer to our decision.

If the Danish Medicines Agency is unable to acquiesce to AstraZeneca's request for general conditional reimbursement, AstraZeneca suggests that the Reimbursement Committee, in collaboration with the relevant clinical companies, draft clear criteria stating when single reimbursement can be applied for and granted.

Single reimbursements are managed in accordance with the provisions set out in Section 145 of the Danish Health Act and Section 6 of the executive order or reimbursements. If a need should develop for determination of further guiding criteria for single reimbursement, the Danish Medicines Agency will make such determination according to usual practice.

Eisai states that the company is going to lower the price of rabeprazole by 40%. We refer to our comments on prices stated in our decision.

Eisai also states that rabeprazole works faster than the other PPIs, has fewer drug interactions, that their tablet is smaller etc. We refer to the Reimbursement Committee's reference to the National Recommendation List as well as the Danish College of General Practitioners' clinical guideline on dyspepsia.

Søren Cordt Møller, general practitioner specialist, expresses concern about removal of the reimbursement for H2 receptor antagonists, which he promotes as cheap and in many cases, including in the case of reflux symptoms, more effective than protons pump inhibitors. He also promotes the H2 receptor antagonists in relation to adverse reactions and adverse drug reactions. Furthermore, he states that there are individual patients who need treatment with both groups of medicinal products if the patient is to avoid or does not want an operation.

We refer to the Reimbursement Committee's reference to the National Recommendation List as well as the Danish College of General Practitioners'

clinical guideline on dyspepsia. In those exceptional circumstances where there may be a need for treatment with H2 receptor antagonists instead of proton pump inhibitors, an application can be made for single reimbursement.

The Association of Danish Pharmacies indicates that thorough information initiatives are important.

We agree that comprehensive information for general practitioners, pharmacies and the affected patients is important, and we will launch a broad information initiative, cf. also our decision.

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Price overview for ATC group A02 – drugs for acid-related disorders

Price of treatment for pharmacy-only medicinal products
The prices of treatment stated are per day for prescription-only medicinal products (disp. A and B) and per dose for over-the-counter medicinal products (disp. HA).
The prices are based on the average lowest unit prices (for medicinal products eligible for reimbursement: reimbursement prices) and calculated over six price periods in accordance with the Danish Medicines Agency's guidelines for evaluation and comparison of medicinal products in reassessments of reimbursement status dated 4 July 2006.

The overview contains prices of treatment from the price period which formed the basis of the Committee's recommendation (period 1) as well as updated prices of treatment for the latest six price periods (period 2):
Period 1: first period beginning on 21 September 2009 and last period beginning on 30 November 2009
Period 2: first period beginning on 8 March 2010 and last period beginning on 17 May 2010

Price of treatment for medicinal products in free trade
Some medicinal products in the group have dispensing status HF and are therefore not limited to sales from pharmacies.
Prices are determined locally by the sales outlet, and the companies are not obliged to report a price for these medicinal products to the Danish Medicines Agency. The prices of treatment which have been listed below for medicinal products with dispensing status HF are per dose and have been calculated on the basis of the prices which pharmacies have reported to the Register of Medicinal Product Statistics at the Danish Medicines Agency for the share sold on prescription.

The overview contains prices of treatment from the price period which formed the basis of the Committee's recommendation (period 1) as well as updated prices of treatment for the latest six price periods (period 2):
Period 1: 3 August 2009 to 25 October 2009 (corresponding to six price periods)
Period 2: 28 December 2009 to 21 March 2010 (latest validated figures, corresponding to six price periods)

Cimetidine was taken off the market on 25 February 2008, and the prices listed below are from the period between 3 December 2007 and 24 February 2008.

ATC	Active substance/group	Disp.	Dose used	Disp. form	Strength(s)	Price of treatment (DKK) Period 1	Price of treatment (DKK) Period 2
A02A	**Antacids**						
A02AB04	Dihydroxyaluminium sodium carbonate	HF	1-2 tabl. of 400 mg [1]	Tablets	400 mg	0,71 - 1,42	0,76 - 1,52
A02AD	Aluminium aminoacetate + magn. oxide	HF	1-3 chewing tablets [1]	Chewing tablets	500 mg + 100 mg	0,58 - 1,74	0,59 - 1,77
	Calcium carbonate + magn. hydroxide	HF	1-2 chewing tablets [1]	Chewing tablets	449 mg + 104 mg	0,80 - 1,60	0,98 - 1,95

	Aluminium hydroxide + magn. carbonate	HF	700-3,000 mg [1]	Chewing tablets	700 mg/1,100 mg	0,98 - 3,22	1,00 - 1,16
		HF	700-3,000 mg [1]	Oral susp.	150 mg/ml	0,85 - 3,40	0,86 - 3,45
	Aluminium hydroxide + magnesium oxide	HF	1-2 chewing tablets [1]	Chewing tablets	265 mg + 195 mg	0,93 - 1,86	0,93 - 1,85
		HF	5-10 ml [1]	Oral susp.	110+40 mg/ml	1,25 - 2,50	1,32 - 2,64
A02BA	**H2 receptor antagonists**						
A02BA01	Cimetidine	HF	400-800 mg [3]	Tablets	400 and 800 mg	1,98 - 2,07	Removed: 25.02.2008
A02BA02	Ranitidine	HF	300 mg [2]	Tablets	150 and 300 mg	4,26	3,96
			300 mg [2]	Effervescent tabl	300 mg	8,23	7,85
A02BA04	Nizatidine	B	300 mg [2]	Tablets	150 mg	6,90	Removed: 28.12.2009
A02BB	**Prostaglandins**						
A02BB01	Misoprostol	A	0.8 mg [3]	Tablets	0.2 mg	13,68	13,96
A02BC	**Proton pump inhibitors**						
A02BC01	Omeprazole	HA	10 mg [5]	Ent.-cov. tabl./ca	10 mg (up to 56 pcs.)	1,79	2,29
A02BC01	Omeprazole	B	20 mg [4]	Ent.-cov. tabl./ca	10 (>56 pcs.), 20 and 40 mg	0,65	0,59
A02BC02	Pantoprazole	HA	20 mg [5]	Ent.-cov. tabl.	20 mg (up to 28 pcs.)		1,89
A02BC02	Pantoprazole	B	40 mg [4]	Ent.-cov. tabl.	20 (>28 pcs.) and 40 mg	0,73	0,55
A02BC03	Lansoprazole	HA	15 mg [5]	Ent.-cov. caps.	15 mg (up to 56 pcs.)	0,80	1,07
A02BC03	Lansoprazole	B	30 mg [4]	Ent.-cov. caps.	15 (>56 pcs.) and 30 mg	0,91	1,16
A02BC04	Rabeprazole	B	20 mg [4]	Tablets	20 mg	10,71	8,39
A02BC05	Esomeprazole	B	20 mg [4]	Tablets	20 and 40 mg	5,37	9,43
		B	20 mg [4]	Ent.-cov. granula	10 mg	24,04	24,52
A02BX	**Other drugs for ulcers and gastroesophageal reflux (GERD)**						
A02BX02	Sucralfate	HF	4,000 mg [3]	Tablets	1,000 mg	10,28	11,89
		HF	4,000 mg	Oral solution	200 mg/ml	12,80	12,77
A02BX13	Alginic acid	HF	1-3 chewing tablets [1]	Chewing tablets		1,41 - 4,23	1,42 - 4,25
		HF	10-20 ml oral susp. [1]	Oral susp.		2,30 - 4,60	2,30 - 4,60

Medicinal products for injection

ATC	Active substance/group	Disp.	Dose used	Disp. form	Strength(s)	Price of treatment (DKK Period 1	Price of treatment (DKK) Period 2
A02BA02	Ranitidine	B	300 mg [3]	Inf. conc.	25 mg/ml	7,99 / ml	8,00 / ml
A02BC01	Omeprazole	B	20 mg [3]	Inf. fluid	40 mg 5 vials	136,04	136,23

A02BC02	Pantoprazole	B	40 mg [3]	powd f/inj.	40 mg 5 pcs.	129,60	129,78
A02BC05	Esomeprazole	B	30 mg [3]	powd. f/inj.+inf.	40 mg 10 vials	107,38	107,53

Notes/explanations:

1	Recommended dose (Medicin.dk). These medicinal products are used as required, and no DDD value has been determined.
2	Equieffective dose (National Recommendation List)
3	DDD value (WHO)
4	Equieffective dose for the indication healing (National Recommendation List)
5	Recommended dose (Medicin.dk). These medicinal products are used as required.

[redacted]