

Public report of the **629th** meeting of the Medicines Evaluation Board,  
*Thursday 23 November 2006*

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<sup>1</sup> Anatomic Therapeutic Chemical Classification System (ATC code) devised by the World Health Organisation (WHO)

c B G  
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M E B

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**MEB members**

Dr J.F.F. Lekkerkerker – *chairman*  
 Prof. J.T. van Dissel  
 Dr A.A.M. Franken  
 Prof. Y.A. Hekster  
 Prof. A.W. Hoes  
 Dr P.A.F. Jansen  
 Prof. G.J. Mulder  
 Dr C. Neef

Prof. A.F.A.M. Schobben – *deputy chairman*  
 Dr M.F. Peeters  
 Prof. J.M. van Ree  
 Prof. H. Schellekens  
 Prof. J.H.M. Schellens  
 Prof. P.A.B.M. Smits  
 Dr J.A.J.M. Taminiau

**Management / Secretariat**

A.A.W. Kalis  
 Dr R.T.W. Meijer  
 F.W. Weijers  
 E. van Galen  
 J.A. Lisman  
 J.W.A. Münninghoff  
 H. Stevenson

K.H. Doorduyn – van der Stoep  
 D.S. Slijkerman  
 Dr S.M.J.M. Straus  
 A. Torqui  
 A.I.M. Wesseling  
 D.F.J. van Wijland - Slegers  
 Dr B.J. van Zwieten – Boot

**Experts as referred to in Article 8 of the decree governing the Medicines Evaluation Board who were present at the meeting**

Dr G.J.A. ten Bosch  
 N. Brouwer  
 Dr C. Brouwer  
 E.G.J. Carrière  
 Dr A.J. Croockewit  
 Dr A.J.A. Elferink  
 Dr C.C. Gispen – de Wied  
 Prof. P.A. de Graeff  
 C. Herberts  
 F. Holtkamp  
 Dr J.W. van der Laan  
 Prof. H.G.M. Leufkens

Dr H.A.I.M. van Leusden  
 A.R. van der Linden  
 Dr A.K. Mantel – Teeuwissen  
 Dr J.M. van der Nat  
 Dr J.H. Ovelgönne  
 D.A. van Riet – Nales  
 Dr T.G.J. van Rossum  
 Dr S. Simonian  
 Dr C. Versantvoort  
 E.F.W. van Vlijmen  
 Dr T.D. Wohlfarth

**For the report:**

B.J. Klijn

629th meeting of the MEB  
on 23 November 2006  
Agenda item 1.1

### **Opening**

The chairman opened the 629th meeting of the Medicines Evaluation Board and welcomed those present. A special welcome was extended to Mr Holtkamp, clinical evaluator at Groningen, Ms Brouwer of the Centre for Quality of Chemical-Pharmaceutical Products (KCF) and Mr Torqui, authorisation coordinator for Pharmacotherapeutic group III. They had not previously attended a meeting of the MEB.

629th meeting of the MEB  
on 23 November 2006  
Agenda item 1.1a

### **Conflicts of Interest**

*None of those present reported any 'Conflicts of Interest'.*

629th meeting of the MEB  
on 23 November 2006  
Agenda item 1.2

### **Setting the agenda**

The agenda was set without any amendments.

629th meeting of the MEB  
on 23 November 2006  
Agenda item 1.3a

### **Amended report of the 627th meeting of the MEB**

A number of textual amendments were proposed and implemented.

629th meeting of the MEB  
on 23 November 2006  
Agenda item 1.3b

### **Draft report of the 628th meeting of the MEB**

*No comments.*

**Announcements**

Absent with notice: Mr Rosmalen and Ms Janse – de Hoog.

It was agreed that electronic meeting documents will be sent to MEB members' office e-mail address. If no office e-mail address appears on the MEB list, the documents will be sent to members' private e-mail addresses. Therefore, *no* meeting documents or meeting requests will be sent to the MEB e-mail address. The MEB e-mail addresses cannot be used because the electronic post-boxes cannot be opened due to technical problems. Moreover, not all MEB members use these addresses.

It was agreed internally that all forwarded mail for the MEB meeting will be sent via the 'College en Q' office post-box and approved by the secretary of the MEB. However, the chairman received a request asking whether certain mailings may be dispatched to MEB members from the FT groups themselves without prior permission from the secretary. The MEB advised against this. It was **resolved** that the e-mailings will be sent after approval by the secretary or the chairman unless otherwise agreed in the 'Q' consultations or in the MEB meeting. The sole exception to this rule is that in the case of withdrawals, hospital pharmacies will always be asked whether certain medicines can be withdrawn or an authorisation can be deleted.

The MEB is of the opinion that the magnitude and frequency of the electronic mailings is such as to jeopardise the proper functioning of the e-mail system. The same applies to the technical support system: it is not possible to integrate the mailings into the electronic agenda. In addition, the amount of e-mail (and its volume) is increasing far too much, which means that the MEB is unable to perform its duties properly. The large quantities of mail block up MEB members' mailboxes; it is impracticable to receive ten long attachments which all have to be transferred to a carrier or printed out. This point was actually discussed during the previous meeting in Utrecht, and the secretariat promised to mend matters. The secretariat proffered its apologies to the MEB and promised to put this item at the top of the agenda during the following Monday's management meeting. It was **resolved** that the chairman will approve the (exceptional) mailings for the time being.

During the anniversary celebrations for the Medicines Bulletin, the chairman made the acquaintance of Belgian medicines committee member Professor Marc Demeyere. He is very interested in the way the MEB is run, and since this procedure differs from that in Belgium, Prof. Demeyere would like to attend an MEB meeting. The MEB **resolved** to agree to this because there are no impediments among the Boards to attending one another's meetings.

The agenda for the MEB meeting for 21 December is limited. It was proposed to hold the meeting anyway and to start at 14.00 hours as usual. The meeting will end at about 17.00 hours and the dinner will not be held as a result. However, MEB members will be able to attend the Christmas lunch, which will be held on Wednesday 20 December: invitations will be sent by e-mail in the near future. Transport to and from the establishment can easily be arranged.

With regard to the reorganisation and the introduction of the new ICT system, the meeting was informed that both projects are well under way. However, there is a certain amount of delay because there are a number of problems regarding delivery of the system in accordance with the required specifications. This means that the sample will not be delivered for a couple of weeks, which in turn will result in the reorganisation having to be postponed as well. After consultation with the Works Council, it was decided to relocate the various employees permanently to their new places at the end of March, although work in the new grouping will probably commence at an earlier date.

**Pharmacovigilance Working Party (PhVWP) Report – meeting 13-14 November 2006**

During the past few weeks, four reports have been received of deaths after an *influenza vaccination*. The first case occurred at the beginning of November and concerned an 88-year-old man with a large number of cardiovascular risk factors and the appropriate medication. He died about half an hour after receiving the influenza vaccination. The second case concerned an 80-year-old woman with hypertension and serious decompensatio cordis, who died within five minutes of receiving the influenza vaccination. Both these deaths have been extensively assessed and evaluated as being extremely unlikely that they are related to the vaccination. Two new cases were reported at the end of last week: the first case concerned a 58-year-old man whose sole risk factor was COPD, who was vaccinated at 16.00 hours and found dead at 18.10 hours. The second case concerned a 53-year-old man with COPD/asthma who was vaccinated in the afternoon and found dead the same evening at 21.45 hours. These four cases were discussed extensively, and in view of the background mortality, among other factors, the MEB established on the basis of this evaluation that it seems extremely improbable that these cases are causally related to the influenza vaccinations. The Ministry subsequently resolved that there was no need to adjust the influenza vaccination programme.

Although there are no immune reactions to influenza, it is possible that someone reacts to the chicken proteins. This can even provoke violent reactions, although it should of course be accompanied by a clinical picture of e.g. oedema and skin rash. After evaluation of these cases, allergic or anaphylactic reactions were ruled out and no connection was established. No deaths were reported in 2005, although four were reported in 2004. With regard to three of these deaths, the persons were known to have been vaccinated at an earlier date, and some had even been vaccinated a number of times previously. No post-mortem was carried out on any of the four deceased persons, but another option would be to examine 'stress elements' in organs, blood or spinal fluid. Post-mortem examinations can be carried out which would give information on any anaphylactic reactions, and a protocol can be drawn up for this purpose.

Reporting the adverse events of vaccines is still not regulated as well as it should be. This is a reason for urging once more for improved registration, since adverse events should be reported to the Netherlands Pharmacovigilance Centre (Lareb). The MEB bears joint responsibility for this, and it has not been carried out systematically to date. Reports are obtained through the state vaccination programme (RVP) and reports made to Lareb. Although the MEB has access to the Lareb reports, it does not have access to those of the RVP, so this will have to be discussed once again. Due to a recommendation from the Council for Public Health and Health Care, the National Institute for Public Health and the Environment is making every effort to increase cooperation in this regard with Lareb's Teratology Information Service and vaccination department. There are far more reports on medicines than on vaccinations.

The Assessment of the Community System of Pharmacovigilance (the so-called *Fraunhofer report*) was also on the agenda. There have been a great many reactions to this, and the report has been discussed in the PhVWP. The main point here is reinforcing the position of pharmacovigilance, which is also a hot topic in the political scene. The EC has informed the PhVWP and the CHMP of the comments, and a number of recommendations have been issued on the basis of these. One of these recommendations is that sufficient funds should be made available for pharmacovigilance and that existing facilities should be used. In addition, organisation and decision-making should be simplified, whereby further amendment to the legislation is required. Proper communication and a strong degree of involvement on the part of all parties are also of considerable importance in pharmacovigilance, including the risk communication aspects. It was clear that the EC did not regard the report as end point, but as the beginning of European consultations. Moreover, those concerned are aware that independent funding is essential. The MEB evaluates data which is almost entirely supplied by the industry itself, but the PhVWP discussions strongly emphasised that certain issues are involved which will not always be included by all of these industries.



Another point was the development of expertise within the Agencies themselves; the Netherlands is doing well in this regard. Portugal has carried out an investigation and has concluded that it is doubtful whether certain Agencies are capable of assessing a risk management plan at the present moment.

Between 70% and 80% of the risk management plans to be assessed are based on data from the USA. Since this would be an undesirable situation in the future, increasing attention will be devoted within Europe to ways of using European data as well. The EMEA has initiated the setting up of a platform and will be inviting all the 'data clubs' to attend.

The PhVWP report mentions an important publication in *Neurology* on overdosing of **ergotamines**.

Reports have been made of the effects of **oseltamivir** on the central nervous system in children. This data comes from Japan, and the FDA has meanwhile been contacted and has sent out a warning. The FDA's conclusion, incidentally, is that the data solely concerns cases in Japan and that no new data or new cases have been submitted to the FDA. These are the same cases discussed in the PhVWP last year, where the conclusion was also published on the website last year.

With regard to **telmisartan**, the report states that simultaneous use of NSAIDs serves to increase the anti-hypertensive effect of telmisartan, although it is always stated exactly the other way round in text books. This point was raised by Italy at the end of the meeting, and will be further discussed in the December meeting. Italy will be compiling a report. A suggestion has been made that it probably exclusively involves acetylsalicylic acid.

The pre-clinicians were pleased with the conclusion that although **ACE-inhibitors** may not be used in the second and third trimesters of pregnancy, there are no problems concerning its use in the first trimester. Finland had brought an expert along who gave an extremely convincing presentation accompanied by satisfactory database research, from which it transpired that all associations with first-trimester malformations cease from the moment that diabetes correction is carried out on the mothers.

**Trasylol** (*aprotinin*) is an old-fashioned product which was authorised at the time for reducing loss of blood after open heart surgery, which in turn reduced the number of blood transfusions needed. Information shows that the medicine is used with extreme caution in heart-surgery centres in the Netherlands. Two observational studies were published at the beginning of this year which demonstrated that more incidents occurred during use (myocardial infarction, cases of renal failure resulting in dialysis, and a slight increase in strokes). These facts had previously resulted in a discussion on this product and also induced the FDA to organise a meeting on 21 September, after which it then turned out that the firm had already started a third study. This firm had obtained new data but did not publish this data. The firm came to the meeting to elucidate the study: it concerns a product that is authorised because it has a more satisfactory effect than a placebo with regard to decreased blood transfusions. However, the adverse events with regard to two other products seem to be more serious. Although these are observational studies, which means there is never 100% certainty, the third study also points the same way. The firm pointed out that there are a great many methodological problems and issues that still need to be dealt with and resolved. The problem is that Germany is the rapporteur for this product, and there is no alternative available there. Germany might come up with a different risk/benefit analysis. Both the UK and the Netherlands incline towards a Referral and requesting a comprehensive risk/benefit analysis.



We note here that the Mangano study (which was also discussed by the FDA Advisory Board) may be criticised on the score of its methodological deficiencies, especially confounders. The same problem apparently occurs in the study conducted by Bayer as well. The conclusion to date (which is shared by the author of the article in the NEJM) is that no conclusions can be drawn, at least not for the time being; at the present moment, it seems preferable to refrain from starting a Referral and to await the definitive data. There are still two randomised trials going on: one of these is being conducted in Leiden and the results are expected to materialise within the next six months. A proposal has been made to temporarily endorse the SPC changes as suggested in the June PhVWP. The other trial (known as the BART trial) is on a much larger scale than the Leiden one, although the results of this trial will not be available until 2008 at the earliest. The fact that the Safety Monitoring Board has not yet discontinued the trial is definitely a good sign. Although it is admittedly true that there are shortcomings attached to the Mangano study, this is often the case in observational studies. However, the study conducted by Bayer itself shows that these shortcomings apply to all three products, not only to the Bayer product. Bayer's final report containing the answers to the questions will be published in January. The study will be requested in order to be able to evaluate it as soon as possible. It will then be discussed in the MEB meeting, but no Referral will be started up as yet.

The first sentence on **atorvastatin** is somewhat carelessly worded: "It transpires from a *post hoc* analysis of the study that patients who have recently had a stroke run a slightly higher risk of having a stroke." This is logical and cannot merely be attributed to the medicine. What they intended to say was that it concerned the results of a study in which the ischaemic stroke decreases and the haemorrhagic stroke increases. The overall risk of stroke was decreased and the firm wanted to include this in the SPC for atorvastatin, but had written a very attractive account of this.

**Yasmin, Yasmin 28, Yira**

RVG 23827 et al

Two reports on Yasmin have been sent to the MEB. The first of these deals with the Euras study and the second one with the Ingenix study. The latter study is also limited in value: almost 90% of the cases were dropped from the study for various reasons, although these are often non-medical reasons. The firm has been asked to send on this data in order to make it clear on what grounds the final number of cases were selected. The data already submitted does not show any differences between Yasmin and other contraceptives with regard to the risk of venous thrombosis.

We note here that in the conclusion (the first bullet point), it would be better to refer to 'potential cases' than to 'cases' that have been excluded. The term 'propensity score' (on the same page) should be used because as it now stands, it is unclear that the firm actually used this method. Moreover, the tone of the report implies that the firm is untrustworthy; the tone should be a little milder.

The Euras study was conducted in Europe and is the consequence of a 'commitment' on the part of the firm at the time of authorisation. In this large-scale study, Yasmin is compared with second-generation oral contraceptives and with other OCs. It was concluded that no increased risk of VTE has been demonstrated. It might be expected that the clinical end point might be influenced on the basis of differences in effects on the haemostatic factors, as seems to be the case for the third generation of contraceptive pills. However, this study shows no difference between Yasmin and second-generation contraceptive pills which are thought to pose the lowest increased risk of thrombosis. Nor is there any increased risk vis-à-vis the group of other contraceptive pills, which primarily comprise third-generation pills.

The firm's report originally contained a power calculation which was barely comprehensible. The essential point is that the highest confidence interval of the relative risk must be under 2. But in that case, we also have to know how they arrived at the power. This has meanwhile been altered, and the MEB considers the report to be satisfactory. The evaluator will draw up an SPC proposal which will be presented at the Pharmacovigilance Working Party meeting because the Netherlands is the RMS for Yasmin.

**Public Assessment Reports (PAR)****Sodium valproate** chrono 300 and 500 mg;

RVG 29985/6

Text deleted in the report means that the firm would like this text to be removed. The firm has made use of the opportunity to indicate text that should be confidential. A great deal has been deleted from the tables on page 7, although it is completely unclear why this data should not be published. Before the public assessment report is published, the firm will be given a chance to comment. This does not mean that the MEB has to accept the firm's remarks, and in this regard, the phrase stating that 'the company has checked this report' on page 1 should be amended. At the present moment, one receives the impression that the firm is in agreement, which surely cannot be intended. It would be better to say that 'the company has commented on the presence of confidential information'. It was **resolved** to alter the template accordingly.

A statement is made on the stability of the component on page 3: this information is unnecessary in a PAR. Information on the stability of the end product is useful information for users, but the stability of the component is of no value. It is true that the same active components manufactured by various suppliers do not always have the same storage life, although this does not affect users very much because they are only concerned with the end product.

The report states that the tablets are breakable. It should therefore also state (since the tablets in question are retard tablets) that dissolution of the half-tablets is correct: this will be added to the report.

The tables containing a number of deletions by the firm should either be completely omitted while stating the conclusion, or reproduced in their entirety. It was decided at an earlier date to include these tables and the MEB approves this decision.

The top paragraph states that "bioequivalence was however not fully demonstrated". The firm understandably has some difficulty with this, since it means that the product does not comply with the requirement. However, the sentence goes on to say that the product is in the acceptance range between 0.80 and 1.25. The first part of the sentence should therefore be deleted: it is definitely acceptable.

The MEB **resolved** to publish the PAR after the alterations as stated above had been carried out.



**Simvastatin** PSI 10, 20 and 40 mg;

RVG 29097-9

The numbers in the text and the table on page 5 do not tally: the table should include the confidence intervals as well as the range. The table will be altered accordingly and submitted once more to the MEB before the PAR is published.

**Estradiol** 2 mg

RVG 29985/6

The phrase "needed for sufficient bioavailability" should be worded differently. This information is important because it concerns a requirement for the component. The numbers in the table should also be critically examined.

On page 4, the firm has deleted the information that the study in question was carried out on 20 volunteers, but this information should be left in. This was **resolved** by the MEB.

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**Any other business**

a) It would seem that the product *cisapride* will finally be taken off the market; the firm has stated that this product will no longer be available. However, this refers solely to the tablets, since the suspension will remain authorised and may be obtained under the same conditions as previously. The firm admittedly wanted to cross off the suspension as well, but the MEB lodged a protest against this and proposed discussing the issue in the paediatrics feedback group. The firm of Janssen agreed to await the verdict of this feedback group. The issue is bound to come up again.

b) Talks on a stent were held this morning with a '**Notified Body**'. Firms are becoming increasingly aware that stents have to comply with certain requirements.

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**Conclusion**

The chairman closed the meeting at 18.51 hours by thanking those present for their contributions.