

**Unedited Report of the Supplementary
Meeting of the Expert Committee on the
Selection and Use of Essential Medicines**

15 January 2010

Geneva



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List of participants

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Mr Andy Gray (Rapporteur), Department of Therapeutics and Medicines Management, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Congella, South Africa

Member of the Committee participating via video conference:

Professor Rohini Fernandopulle, Department of Pharmacology, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka

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Dr Hans V. Hogerzeil, Director, HSS/EMP

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Declaration of interests

All members of the Expert Committee completed the standard WHO form for declaration of interests prior to the meeting. At the start of the meeting, all participants were asked to confirm their interests, and to provide any additional information relevant to the subject matter of the meeting.

The following interests were declared:

Mr Andy Gray reported having accepted travel support from AstraZeneca, Fresenius Kabi and Aspen Pharmacare to attend continuing education events as a guest speaker, and also receiving research support grants from various donors of antiretroviral medicines used in ACTG and IMPAACT trials and from Gilead Sciences. He also reported being a member of the Scheduling and Naming Expert Committee of the South African Medicines Control Council and being a director of a government funding agency for biotechnology. These were not considered conflicts of interest in relation to the subject of the meeting.

Dr Gregory Kearns reported being the Principal Investigator, on a NIH grant to Children's Mercy Hospital for projects not related to antivirals and being a Member, Clinical Pharmacology Advisory Committee, Food and Drug Administration, Department of Health and Human Services, USA. These were not considered conflicts of interest in relation to the subject of the meeting.

Dr Anita Zaidi reported receiving research funding in the past three years from Wyeth in the area of pneumococcal Surveillance for her research unit, now completed. This was not considered a conflict of interest in relation to the subject of the meeting.

Dr Lisa A. Bero, Professor Noel Cranswick, Professor Rohini Fernandopulle and Dr Alar Irs reported no conflicts of interest.

Introduction

A Supplementary meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines took place in Geneva on 15 January 2010.

The meeting was opened on behalf of the Director-General by Dr Hans V. Hogerzeil, Director of the Department of Essential Medicines and Pharmaceutical Policies (EMP). He stated that the evidence in relation to essential medicines is changing rapidly and that the WHO needs to take this into account when planning its activities. He further noted that this session was the first ever supplementary session of the Expert Committee, following approval in principle by the Director-General of the proposals for such meetings from the March 2009 meeting. He noted that apart from the shortened timeline, the main change to the normal committee meeting processes was the use of tele/video conference links to hold the meeting. All other procedures for the Expert Committee had been followed, including posting documents on the web site, together with the rounds of review and comments prior to the meeting.

Dr Hogerzeil briefly explained some aspects of the Committee procedures. He stated that the Committee is not a representative one; all members participate in their own personal capacity and are not allowed to take instructions from any government or any other authority. He also noted the increasing attention being paid to potential conflicts of interest in relation, in particular, to influenza policies and expressed confidence in the procedures followed in regard to this meeting. The Committee followed its usual procedures in relation to reporting and evaluation of conflicts of interest of members, as summarized in this report.

Section 6.4.3: Other antivirals

Amantadine and rimantadine, oseltamivir, zanamivir (Inclusion)

At its March meeting in 2009, the Expert Committee considered four applications for antivirals to be included in the WHO Model List of Essential Medicines: amantadine, rimantadine, oseltamivir and zanamivir.

The Committee's decisions at that meeting were:

'The Committee noted that the costs of amantadine and rimantadine vary but are generally cheaper than the neuraminidase inhibitors. Overall the evidence to support the effectiveness of any of the four antivirals for treatment of avian influenza remains very low quality. The effect of these medicines on seasonal influenza is better established, but may be of less importance. When used for treatment of individual cases of H5N1, the cost is low but in the context of seasonal influenza, they have not been accepted as cost effective. On balance, the potential advantage of the inclusion of any of them on the List would be to perhaps increase availability and decrease price. This would be critical in the context of responding to a pandemic, but the pandemic preparedness plans already include stockpiling of antivirals (often donated.) It is not clear that addition of the medicines to the List would enhance this access programme.'

After consideration of these factors, the Committee recommended not including any of the antivirals on the List at the present time. However the Committee endorsed the proposal for an emergency meeting mechanism to consider one or more, including for paediatric use, should a pandemic occur.'

The situation since the March 2009 meeting has changed in that a pandemic has indeed occurred. The pandemic influenza virus, pH1N1, is sensitive to neuraminidase inhibitors, but not to the M2 inhibitors. There has been considerable debate about the role of oseltamivir and zanamivir in treatment and prophylaxis of infection due to the pandemic virus, which has for the present almost completely replaced seasonal influenza virus as the main circulating strain.

WHO issued treatment guidelines in August 2009 that recommended use of oseltamivir and zanamivir for treatment in certain patient groups, particularly for those patients presenting with complications or severe disease. This recommendation was based on assessment of the randomized trial data represented to the Expert Committee in March 2009, plus an evaluation of observational studies that suggest that antivirals may reduce the rate of clinically relevant complications of influenza. In those guidelines, oseltamivir was considered as the first option for treatment.

An update of these guidelines has been prepared and the draft recommendations from the guideline panel, which met on 13-14 January 2010, were provided to the Expert Committee members. The updated evidence summaries prepared for the guideline meeting, including the GRADE evidence profiles summarizing available evidence, were also provided to the Expert Committee.

Since March 2009, the registration information for oseltamivir and zanamivir for use in children has been amended by both the US Food and Drug Administration and the European Medicines Agency. Generic versions of oseltamivir have been registered in a number of countries and a number of oseltamivir products have been prequalified for UN procurement by WHO. There have been no changes in the regulatory status to amantadine and rimantadine as far as the Committee has been able to determine.

Evidence summary

A full update of the evidence available in relation to the four antivirals, including observational studies (1, 2, 3, 4, 5) relating to use of the antivirals in the context of the pandemic has been prepared for the guideline panel and circulated to the Committee members. The Committee noted the following:

- There are no new data from randomized trials for any of the four antivirals under consideration.
- The majority of randomized trials are in the healthy adult population; there is one systematic review of trials in children (6).
- The majority of the randomized trials do not report clinically relevant outcomes such as development of pneumonia, hospitalization or mortality. The only published analysis with these data is a report of a pooled analysis from a set of data from Roche [published as Kaiser et al. (7)]. This study was excluded from the update of the

Cochrane Review [published as Jefferson et al. (8)] as the data from all of the individual trials were not made available to the authors of the Cochrane Review. The exclusion of this study and the possibility of publication bias in the trials conducted by Roche has been the subject of discussion in the BMJ articles (9, 10, 11) published with the Cochrane Review.

- The observational data are summarized in the updated evidence summary for the guideline panel (12, 13, 14) and also (15, 16, 17, 18, 19, 20, 21, 22, 23, 24) and, in the population studied, including higher risk groups, suggest a significant benefit of treatment with oseltamivir in terms of reduction of hospitalization and occurrence of pneumonia. Three observational studies (12, 23, 25) suggest benefit in terms of reduction in mortality. There are fewer data for zanamivir and no current observational studies of amantadine or rimantadine that are relevant.
- Adverse effects of all four antivirals are well characterized. The only additional data from March 2009 are the observation that the neuropsychiatric effects that have been reported in relation to oseltamivir have not been reported so far in studies outside of Japan, notwithstanding extensive use in a number of countries over the last six months.
- The data from children has been summarized in the evidence update. In addition, an unpublished analysis (26) of information relating to dosing of oseltamivir in children under 2 years has been provided for the guideline panel.

Considerations of the Expert Committee

The Committee noted that there was no change to the cost and availability information for amantadine and rimantadine from March 2009. With respect to oseltamivir, it was noted that the cost had generally come down and was variable as multiple manufacturers have registered and also prequalified products through the WHO-UN programme, and donation programmes are in place. For zanamivir, no change in cost or the low availability of the inhaled preparation was noted, although this medicine is also included in the WHO-UN Prequalification Programme expression of interest and at least one product has been pre-qualified. The Committee was informed that an intravenous preparation of zanamivir was available in a limited number of countries as an experimental product, but it was not yet licensed anywhere.

The comments received from Expert Panel members and others on the proposals posted on the web site were noted by the Committee. Generally, the comments highlighted the absence of randomized controlled trial evidence directly relating to the evidence for effectiveness and safety of all antivirals in the pandemic, as well as raising questions about whether any antiviral would meet the definition of an essential medicine.

The Committee considered that:

The evidence from randomized clinical trials for all antivirals has not changed substantially since March 2009. However, there has been more experience of the use of oseltamivir since the declaration of the pandemic, and the observational data resulting from this use provide some estimates of effectiveness. Since March 2009, there is also more evidence of the relative

safety of oseltamivir in a range of patient and age groups, with no evidence of harm. The updated WHO recommendations concerning use of oseltamivir for treatment of seriously ill patients or those in higher-risk groups are based on these data. Oseltamivir resistance has been described, very rarely, for the current pandemic H1N1 strain. In these cases, the virus has remained susceptible to zanamivir. However, there remain concerns that increasing use of antivirals will lead to increased resistance.

Based on the available evidence of the potential benefit of oseltamivir in specific patient groups and the expected prevalence of pandemic H1N1 in the coming seasons, the Expert Committee agreed to add this medicine to the Core List. The Committee specified that the List should include the following notes: oseltamivir should be used only in compliance with the WHO treatment guidelines, i.e. (1) for treatment of patients with severe or progressive clinical illness with confirmed or suspected influenza pandemic (H1N1) 2009, (2) for the treatment of patients with confirmed or suspected but uncomplicated illness due to pandemic influenza virus infection who were in higher risk groups, most notably for pregnant women and children under 2 years of age.

Oseltamivir will be listed in the following dosage forms:

- Capsule: 30 mg; 45 mg; 75 mg.
- Oral powder: 12 mg/ml.

The Committee noted the ongoing need for age-appropriate dosage forms for children, including neonates.

The WHO treatment guidelines will be reviewed in the early Northern winter of 2010, and the Committee therefore recommended that its decision to include oseltamivir should be reviewed at the March 2011 scheduled meeting of the Expert Committee. This scheduled review will also be noted in the Essential Medicines List.

Evidence for benefits of zanamivir in this pandemic is very limited and in the current situation, amantadine and rimantadine are ineffective. The Committee therefore decided not to include zanamivir, as currently, it may only be required in a limited number of circumstances, such as in patients who are found to have infection due to pandemic H1N1 that is resistant to oseltamivir. The evidence for its effectiveness was considerably less than the evidence for oseltamivir. The inhaled dosage form is also more difficult to use in patients presenting with severe or progressive illness and cannot be used in children under 5 years.

The Committee confirmed the decision of March 2009 in relation to amantadine and rimantadine, and recommended that they should not be included on the WHO Model List of Essential Medicines.

In closing the meeting, the Chair noted that the report of the meeting would be circulated electronically to all members of the Committee for ratification, and it would then be submitted for the usual WHO approval processes by the Secretariat.

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