Thank you for your memo dated 31 January 2013 regarding the applications for the 19th Expert Committee on the selection and use of essential medicines. Our responses concerning Section 6: oseltamivir follow (pages 2-5 of this memorandum).

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**Introduction**

- All currently circulating human influenza viruses are resistant to the influenza antiviral medicines amantadine and rimantadine. The neuraminidase inhibitors (which include oseltamivir and zanamivir) are therefore the only effective antiviral medicines that are widely available.

- Oseltamivir is licensed in more than 80 countries for prophylaxis and treatment for influenza virus infection. It is the only specific influenza treatment suitable for use in children under the age of 5, and in severely ill patients. The US FDA lowered the age for use for treatment to 2 weeks of age in December 2012.

- WHO recommends oseltamivir for treatment of severe or complicated influenza, and for treatment of influenza in patients at higher risk of developing severe disease. WHO does not recommend prophylactic use for seasonal influenza nor for the recent pandemic strain (H1N1 pdm09). WHO does recommend prophylactic use of oseltamivir for persons with a high risk of exposure to avian influenza H5N1 to prevent illness that has a high case fatality rate.

- WHO has prequalified oseltamivir formulations from several companies to facilitate equitable access to the medicine. These are Hoffman La Roche (Switzerland), Cipla Ltd (India) and Strides Arcolab Limited (India).

**WHO Guidelines for use of oseltamivir**

WHO guidelines for treatment of influenza virus infection have been developed in full accordance with WHO’s standards for guideline development, which include systematic and objective retrieval and assessment of evidence, transparency and freedom from bias. These standards are described in WHO’s *Handbook for Guideline Development* and overseen by its Guidelines Review Committee.

WHO first published guidelines for influenza treatment in 2006, with the Rapid Advice Guidelines in Pharmacological Management of Humans Infected with Avian Influenza A (H5N1) Virus. At that time the evidence to support reduction in severe illness and death was very limited, and the recommendations reflected the severity of illness and high mortality associated with these infections. Since then, a number of observational studies on treatment of human infection with avian H5N1 influenza have been published. These have demonstrated a lower mortality rate among patients treated with oseltamivir, compared with those who do not receive antiviral treatment. The most recent of these publications was by Adisasmito et al., from which the following figure is extracted, and Oner et al.
Rapid advice guidelines for the treatment of pandemic H1N1 influenza (H1N1pdm09) were first published in August 2009, and revised in February 2010. In these guidelines WHO recommends use of oseltamivir for the treatment of severely ill patients, and those at higher risk of developing severe or complicated disease. These recommendations took into account the available evidence for efficacy and safety from clinical trials, and from observational data.

After the end of the 2009 pandemic, WHO reviewed its guidelines for clinical management of severe influenza and developed a set of Standard Guidelines that include use of influenza antivirals. These standard guidelines are in the final stage of completion, following a full review of evidence and expert consultation. WHO will continue to recommend use of oseltamivir to treat severely ill patients, and those at higher risk of developing severe or complicated disease.

Additional evidence that has been taken into account in developing these standard guidelines includes:

- A systematic review of observational studies on use of antiviral medicines for treatment of influenza. This review concluded that oseltamivir may reduce duration of symptoms, hospitalization, and mortality compared with no treatment (Hsu et al. 2012).
- Another systematic review and meta-analysis of observational studies of neuraminidase inhibitor treatment of patients with 2009 H1N1 virus infection, primarily oseltamivir treatment, concluded that early initiation of treatment reduced the likelihood of severe outcomes compared with late or no treatment. This review found a reduction in mortality of 65% in patients who were treated early compared with untreated patients (Muthuri et al., 2013).
- Pregnancy or postpartum: antiviral treatment of pregnant women of any trimester with influenza A (2009 H1N1) virus infection has been shown to be most beneficial in preventing respiratory failure and death when started within 3 days of illness onset, but still provided benefit when started 3 to 4 days after onset compared with 5 or more days after onset (Siston et al., 2009).
- A large study showed that starting oseltamivir treatment up to 4 days after illness onset provided benefit in reducing the risk of severe illness compared with later treatment of 2009 H1N1 (Yu et al., 2011).
- Another study of critically ill patients and fatal cases with 2009 H1N1 virus infection reported that antiviral treatment with a neuraminidase inhibitor was associated with improved survival compared with untreated patients, and while early treatment conveyed the most benefit, patients who started antiviral treatment up to 5 days after illness onset had improved survival compared with untreated patients (Louie et al., 2012).

Other nonclinical information that supports the use of oseltamivir in reducing hospitalization and death includes:

- An ecological study revealed that sufficient national supply of influenza antivirals (NAIs) reduced mortality during the 2009 pandemic (Miller et al., 2012).
- During the 2009 influenza pandemic, Japan, where NAIs are routinely used for treatment of influenza after point-of-care rapid diagnostics, and where the highest per capita use of NAIs showed the lowest mortality among other developed countries (10-fold) (WER http://www.who.int/wer/2009/wer8446.pdf)
- A report from the Canadian Institute for Health Information on the impact of the H1N1 pandemic on Canadian hospitals showed a relative reduction in admissions to intensive care units coincident with peak use of antiviral medicines.
In summary, very few options are available for the treatment of severe or complicated influenza virus infections. Oseltamivir is the only widely available medicine that is effective against currently circulating strains, and that can be used in young children. WHO therefore recommends this medicine for treatment of severely ill patients, and those at higher risk of developing severe or complicated disease. WHO has taken measures to ensure equitable access to oseltamivir through prequalification of products from different companies, and through its inclusion in the Model List of Essential Medicines. With the continued circulation of seasonal influenza viruses that can cause severe illness and death (see below) and continued sporadic cases of human infections with the avian (H5N1) influenza virus, which carries a high mortality rate, WHO considers oseltamivir to be an essential medicine.

While it is recognized that randomized clinical trials generally represent the highest quality of evidence, it remains that case that few such studies exist on influenza antivirals that address the important public health outcomes of severe disease and mortality. With influenza antivirals now widely recognized as a standard of care in such situations, it is unlikely that such data will be available in the future. WHO therefore must consider a wider range of evidence, in order to provide sound advice and guidance.

**Current influenza epidemiology**
Seasonal influenza epidemics continue to cause morbidity and mortality, despite the availability of vaccines. WHO collates and publishes epidemiological data on a regular basis (see http://www.who.int/influenza/surveillance_monitoring/updates/latest_update_GIP_surveillance/en/index.html ). Example data from the current Northern Hemisphere influenza season include:

- 3010 influenza-associated hospitalizations have been reported in Canada, of which 13.3% were children aged 0-4 years. Since the beginning of the 2012-13 season, 203 deaths have also been recorded.
- In Europe the proportion of patients hospitalized with severe acute respiratory infection (SARI) who tested positive for influenza has been increasing, mainly on account of influenza A(H1N1)pdm09 viruses. Among cases whose ages were reported, most were in the 0-4 age group.
- Seasonal epidemics of influenza have been evident in parts of Africa and Asia.
- Both the H1N1pdm09 and H3N2 viruses have been circulating globally and continue to cause significant health effects in different parts of the world.
- Several countries in WHO’s Eastern Mediterranean Region have been deeply affected by the H1N1pdm09 during 2012/13 season. The clinical and epidemiological description of the epidemics is similar to that observed during the pandemic period, i.e. rapid clinical deterioration in previously healthy persons, requiring hospitalization, and with most deaths occurring mainly in non-elderly or non-high risk populations. These reports were received from Jordan, Palestine, Yemen, Iraq and most recently from Morocco.

Avian influenza H5N1 continues to circulate and is considered endemic in poultry in China, Vietnam, India, Bangladesh and in Egypt. Human cases and deaths have been reported from these countries. Most circulating H5 viruses are known to be resistant to the other class of the antivirals (amantadine and rimantadine) while the great majority of avian viruses that are considered to threaten human health (HPAI H5, H7 and H9) are known to be sensitive to neuraminidase inhibitors, including oseltamivir.

From 2003 through 15 February 2013, 620 laboratory-confirmed human cases with avian influenza A(H5N1) virus infection have been officially reported to WHO from 15 countries,
of which 367 have died. Since the last update on 16 January 2013, ten new laboratory-confirmed human cases with influenza A(H5N1) virus infection have been reported to WHO.

**Global stockpile deployment**

WHO maintains a global stockpile of oseltamivir, which includes paediatric capsules. The stockpile was originally established to enable rapid deployment of medicine in the event of an influenza pandemic. However, with the recognition that seasonal and zoonotic influenza can cause severe disease and death, WHO supplies medicine from the stockpile to low-income countries in response to requests arising from unexpected incidence of severe influenza.

- Sri Lanka and Bhutan asked WHO for provision of pediatric capsules of oseltamivir from its strategic global stockpile to respond to a surge of severe infection by the virus in 2011. WHO released the medicine after risk and the populations' vulnerability assessment.
- In response to the countries' request in Q1 2013 oseltamivir, including pediatric capsules, was distributed to Yemen and Iraq.

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1 Communicated with Hoffman-La Roche, February 2013
2 TAMIFLU Label information [http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021087s062lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021087s062lbl.pdf)
3 WHO F: [qualified products for influenza [http://apps.who.int/medicinedocs/](http://apps.who.int/medicinedocs/)]
14 [https://secure.chi.ca/free_products/H1N1_Alb_final_EN.pdf](https://secure.chi.ca/free_products/H1N1_Alb_final_EN.pdf) accessed 21 Feb 2013.