Application for inclusion, change or deletion of a medicine in the WHO Model List of Essential Medicines

We are a group of authors within an external affiliated non-government organisation, the Cochrane Collaboration, called the Acute Respiratory Infections Cochrane Review Group. We are writing to propose that oseltamivir (Tamiflu) be deleted from the WHO Model Lists of Essential Medicines.

1. Summary statement of the proposal for inclusion, change or deletion

Current Essential Medicines List (EML) states for oseltamivir:


<table>
<thead>
<tr>
<th>6.4.3 Other antivirals</th>
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Oral powder: 12 mg/mL. |
| * potentially severe or complicated illness due to confirmed or suspected influenza virus infection in accordance with WHO treatment guidelines. |


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We propose that oseltamivir be deleted from the list forthwith because of lack of proven public health benefits including,

- lack of proven ability to reduce risk of complications, hospitalisation or death from “confirmed or suspected influenza virus infection”

Oseltamivir was initially listed as a WHO essential medicine soon after the 2009 H1N1 influenza outbreak under what was classified at the time as a public health emergency. At that time there was limited evidence available on the use of oseltamivir in patients with severe influenza. No randomised trials of severe patients had been undertaken and unfortunately this remains the case today. Further, numerous randomised trials on oseltamivir treatment had never been published (this remains true today) and information from observational studies on severely ill patients was limited. While more information became available in 2013 when the Expert Committee last met, since 2013 a number of important research outputs have been published.
In 2014, a systematic review based on a complete set of clinical study reports of clinical trials of oseltamivir used to support applications for regulatory approval was published by independent researchers from the Cochrane Collaboration. This is the first time an independent evaluation of the entire randomised evidence base for oseltamivir has been made public. In 2016 the Cochrane group published a systematic review of observational studies of oseltamivir in hospitalised patients with 2009/A H1N1 influenza infection. Also in 2016 an independent group of experts in complex survival analysis from Germany published a re-analysis of a UK observational study of oseltamivir in hospitalised patients with 2009/A H1N1 influenza infection. Manufacturer sponsored studies were also published but these studies added little additional information to that already known in 2013. One exception was a manufacturer sponsored individual patient meta-analysis of observational studies in hospitalised patients with 2009/A H1N1 influenza infection.

As there are no randomised studies of patients with severe influenza we are currently restricted to evaluating observational studies primarily of patients hospitalised with 2009/A H1N1 influenza infection to inform on the benefits of oseltamivir for severely ill patients. However, as is well known, observational studies are more prone to bias than randomised studies hence they require very careful analysis to ensure risk of bias is minimised but also taken into account in how the results are interpreted. Details and references on the recent publications are presented further below.

2. Name of the WHO technical department and focal point supporting the application (where relevant)

This proposal does not come from the World Health Organization (WHO).

3. Name of the organisation(s) consulted and/or supporting the application

This proposal comes from a group of Authors within an external affiliated non-government organisation, the Cochrane Collaboration, called the Acute Respiratory Infections Cochrane Review Group. We published a Cochrane (systematic) review of, first the published literature on the effectiveness of neuraminidase inhibitors (NIs)[1–3], and then the available regulatory information (unpublished Clinical Study Reports, CSRs), on the effectiveness of oseltamivir (a member of the class of NIs).[4-7]. An important strength of our group is our independence from the manufacturer of oseltamivir. This is important because “Reviewers with financial conflicts of interest may be more likely to present evidence about neuraminidase inhibitors in a favorable manner and recommend the use of these drugs than reviewers without financial conflicts of interest” [8].

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

Oseltamivir (Tamiflu); J05AH02

5. Formulation(s) and strength(s) proposed for inclusion; including adult and paediatric (if appropriate).
We are proposing the drug be deleted in all formulations for adults and children.

6. **Whether listing is requested as an individual medicine or as representative of a pharmacological class**

Only oseltamivir out of the whole therapeutic group (neuraminidase inhibitors) is mentioned in the EML.

7. **Treatment details (requirements for diagnosis, treatment and monitoring).**

Capsule: 30mg; 45mg; 75mg (as phosphate); oral powder 12 mg/mL

8. **Information on public health relevance (epidemiological information on disease burden, assessment of current use, target population)**

In 2012, a petition for deletion of oseltamivir from the EML was submitted based on knowledge at the time, which included a 2012 update to a Cochrane review of neuraminidase inhibitors [4]. This review concluded that “the only benefit from treatment with oseltamivir was reduction in the time to first alleviation of symptoms.” In 2014, the updated Cochrane review, including over 100,000 pages of clinical study reports, reported the same small effect upon symptoms, but also reported significant concerns about the harms profile of oseltamivir [5-7].

9. **Review of benefits: summary of comparative effectiveness in a variety of clinical settings.**

Extract on efficacy from the systematic review abstract results [5]:

In treatment trials on adults, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours (95% confidence interval 8.4 to 25.1 hours, \( P<0.001 \)). There was no effect in children with asthma, but there was an effect in otherwise healthy children (mean difference 29 hours, 95% confidence interval 12 to 47 hours, \( P=0.001 \)). In treatment trials there was no difference in admissions to hospital in adults (risk difference 0.15%, 95% confidence interval −0.91% to 0.78%, \( P=0.84 \)) and sparse data in children and for prophylaxis. In adult treatment trials, oseltamivir reduced investigator mediated unverified pneumonia (risk difference 1.00%, 0.22% to 1.49%; number needed to treat to benefit (NNTB) 100, 95% confidence interval 67 to 451). The effect was not statistically significant in the five trials that used a more detailed diagnostic form for “pneumonia,” and no clinical study reports reported laboratory or diagnostic confirmation of “pneumonia.” The effect on unverified pneumonia in children and for prophylaxis was not significant. There was no significant reduction in risk of unverified bronchitis, otitis media, sinusitis, or any complication classified as serious or that led to study withdrawal. 14 of 20 trials prompted participants to self-report all secondary illnesses to an investigator.

In prophylaxis trials, oseltamivir reduced symptomatic influenza in participants by 55% (3.05%, 1.83% to 3.88%; NNTB 33, 26 to 55) and households
(13.6%, 9.52% to 15.47%; NNTB 7, 6 to 11) based on one study, but there was no significant effect on asymptomatic influenza and no evidence of a reduction in transmission.

Since 2012, at least three individual participant data analyses of neuraminidase inhibitors (primarily oseltamivir) potential effect on mortality were published, based on observational data from the 2009 H1N1 experience. Two were published by independent groups [7,9] and found no effect on mortality, whereas the third, published by a group funded by the manufacturer of oseltamivir [10], did report a protective effect of neuraminidase inhibitors. The results of these studies were as follows:

- The manufacturer funded study of oseltamivir concluded: “Compared with no treatment, neuraminidase inhibitor treatment (irrespective of timing) was associated with a reduction in mortality risk (adjusted odds ratio [OR] 0.81; 95% CI 0.70-0.93; p=0.0024) [10]. However this analysis did not take account of the time-dependent nature of exposure to oseltamivir thus introducing immortal time bias [11].

- The first independent study concluded: “After taking account of time-dependent bias and potential confounding variables, competing risks analysis of the IPD showed no evidence that oseltamivir reduced the risk of mortality (HR 1.03, 95% CI: 0.64 to 1.65)” [7].

- The second independent study concluded: “There is no direct effect of NI on the hospital death rate; the hazard ratio (HR) of NI was 1.03 (95%-CI: 0.64–1.66) [9].

Prior to 2014 limited observational evidence suggested a possible large effect of oseltamivir on mortality, for example an odds ratio of 0.23 based on low quality evidence from three small studies [12]. The manufacturer sponsored study summarised above suggests a much smaller effect on mortality (OR=0.81) however that study did not take account of immortal time bias appropriately in the analysis. The two recent independent studies suggest oseltamivir has no beneficial effect on mortality in hospitalised patients. These latter results are consistent with the independent review of the entire randomised evidence base of oseltamivir which concluded there is a modest positive effect on the symptoms of influenza but effects on more clinically important outcomes such as complications of influenza are unproven.

10. Review of harms and toxicity: summary of evidence on safety

Extract on efficacy from the systematic review abstract results [5]:

Oseltamivir in the treatment of adults increased the risk of nausea (risk difference 3.66%, 0.90% to 7.39%; number needed to treat to harm (NNTH) 28, 95% confidence interval 14 to 112) and vomiting (4.56%, 2.39% to 7.58%; 22, 14 to 42).

In treatment of children, oseltamivir induced vomiting (5.34%, 1.75% to 10.29%; 19, 10 to 57). In prophylaxis studies, oseltamivir increased the risk of psychiatric adverse events during the combined “on-treatment” and “off-
treatment” periods (risk difference 1.06%, 0.07% to 2.76%; NNTH 94, 36 to 1538) and there was a dose-response effect on psychiatric events in two “pivotal” treatment trials of oseltamivir, at 75 mg (standard dose) and 150 mg (high dose) twice daily (P=0.038). In prophylaxis studies, oseltamivir increased the risk of headaches on-treatment (risk difference 3.15%, 0.88% to 5.78%; NNTH 32, 18 to 115), renal events with treatment (0.67%, −0.01% to 2.93%), and nausea while receiving treatment (4.15%, 0.86% to 9.51%; NNTH 25, 11 to 116).

Obtaining access to the complete set of manufacturer sponsored clinical study reports has led to new knowledge made public on the potential adverse effects of oseltamivir. Prior to 2014 it was well known that oseltamivir could lead to nausea and vomiting but published reports of other rarer adverse effects were too few to make any robust conclusions. Independent analysis of the entire randomised evidence base has shown long-term exposure to oseltamivir (as can occur in prophylaxis) can lead to neuro-psychiatric adverse effects as well as renal syndromes.

11. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group.

Because any hypothesized benefit on complications, hospitalisations and deaths remains unproven and open to question, a reliable cost-effectiveness calculation is not possible.

12. Summary of regulatory status of the medicine

Summary of major regulatory approvals in the USA, EU, and Japan:

<table>
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<th>Date</th>
<th>Approval Details</th>
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<tr>
<td>10/27/1999</td>
<td>USA approved Tamiflu for treatment of influenza in adults</td>
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<tr>
<td>11/17/2000</td>
<td>USA approved Tamiflu for prophylaxis of influenza in adults</td>
</tr>
<tr>
<td>12/14/2000</td>
<td>USA approved Tamiflu for treatment of influenza in children &gt; 1 year old</td>
</tr>
<tr>
<td>06/20/2002</td>
<td>EMA approved Tamiflu for treatment of influenza in adults</td>
</tr>
<tr>
<td>06/20/2002</td>
<td>EMA approved Tamiflu for prophylaxis of influenza in adults</td>
</tr>
<tr>
<td>12/12/2000</td>
<td>Japan approved Tamiflu capsules for treatment of influenza in adults</td>
</tr>
<tr>
<td>12/24/2001</td>
<td>Japan approved Tamiflu for treatment of influenza in children &gt; 40kg</td>
</tr>
<tr>
<td>07/09/2004</td>
<td>Japan approved Tamiflu capsules for prophylaxis of influenza in adults and adolescents</td>
</tr>
<tr>
<td>01/17/2002</td>
<td>Japan approved Tamiflu oral suspension for treatment of influenza in adults, adolescents and children</td>
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The world’s leading regulatory body, the US Food and Drug Administration, has put on the Tamiflu drug label (full prescribing information) a statement indicating that oseltamivir is not proven to reduce serious bacterial complications from influenza. The prescribing information: “Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. TAMIFLU has not been shown to prevent such complications.”

The FDA has not approved oseltamivir for the reduction of the transmission of influenza.[4] (To assume so is a misreading of the FDA’s approval of the prophylaxis
indication, which was based on a demonstrated reduction in risk of symptomatic influenza, not reduced risk of infection.) See the FDA-approved TAMIFLU label (below), Figure:

Figure: FDA-approved label

http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021087s059,021246s042lbl.pdf


Not relevant to this application

14. Reference list


Signed

Authors of the Acute Respiratory Infections Cochrane Review Group review of neuraminidase inhibitors.
<table>
<thead>
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