

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA158; Oseltamivir, amantadine and zanamivir for the prophylaxis of influenza, and TA168; Amantadine, oseltamivir and zanamivir for the treatment of influenza

Final recommendation post consultation

The technology appraisal programme recommends that, as proposed to consultees, TA158 should remain on the 'static guidance list' and TA168 is transferred to the 'static guidance list'.

1. Background

TA158 was issued in September 2008 and placed on the static list in November 2011.

TA168 was issued in February 2009.

In November 2013, NICE proposed to put TA168 on the static list, taking into account an earlier Cochrane review of regulatory data. The paper stated:

- Cochrane focussed on reviewing clinical study reports of placebo-controlled randomised controlled trials, regulatory comments and reviews of the effects of the neuraminidase oseltamivir and zanamivir for influenza in all age groups, and appraise the trial programmes rather than single studies.
- Cochrane concludes that 'oseltamivir shortens symptoms by less than a day in people with influenza-like illness (ITT population) but there is no evidence of an effect on hospitalisations', and '[however,] we found it difficult to draw hard conclusions regarding the other effects of neuraminidase inhibitors on the efficacy outcomes of key importance in this review (viral transmission and complications of influenza)'.

- These conclusions are in line with those of the health technology assessments underpinning the technology appraisals in this area. Nothing has therefore materially changed in this respect as a result of the Cochrane work.
- Furthermore, the health technology assessments explored the impact of inclusion and exclusion of 'complications' on the results of the economic model, leading to the conclusion that excluding complications only made a difference when combined with changes to other assumptions in the model (e.g. QoL). In these combined scenarios, the ICER increased to >£30k in the 'otherwise healthy' population (see Tables 7.30 and 7.31 page 193 of the Assessment Group report). Importantly, these scenarios remained below £30k in the 'at-risk populations'. These scenarios were discussed in full by the committee and their position (i.e. complications less plausible for otherwise healthy adults) is stated in paras 4.3.13 - 4.3.16 of the FAD of TA168.

Three of the six respondents agreed with the proposal to put the Guidance on the static list, while the other three respondents provided a 'no comment' return. No response was received from the Cochrane collaboration at the time of consultation on the November 2013 review proposal. NICE was subsequently approached by Cochrane indicating that a further review would be published early in 2014.

In light of the subsequent Cochrane review, published in April 2014, NICE consulted with stakeholders in June 2014 as to whether it should review its guidance.

The paper stated: We consider that the results of the Cochrane update are unlikely to change the recommendations of TA158 and TA168.

- First, the population for whom oseltamivir and zanamivir are recommended by NICE is the 'at-risk' group as defined in TA158 and 168. The Cochrane update reports on evidence for healthy adults and children, without providing results for subgroups, including what could be considered as the 'at-risk' population.
- Second, although the effect sizes in terms of symptomatic benefits are perhaps a little lower than was assumed in the analyses performed for NICE in TA168, they are not inconsistent with the range of estimates applied in different scenarios explored for that guidance. In those scenarios more conservative symptomatic benefits (which appear comparable to those reported here) were applied, resulting in oseltamivir as still being cost-effective.
- Furthermore, the Committee noted that in all of the population subgroups, treatment with either antiviral drug was associated with reductions in the average duration of symptoms compared with placebo, although the difference was not statistically significant in all subgroups. The Committee acknowledged that the reduction in duration of symptoms was generally greater for the 'at-risk' population compared with healthy populations.

- Third, although it is more difficult to compare inputs for complications given the different definitions employed in the Cochrane paper and the approach used in the economic model for TA168 (i.e. linking all complications via treatment effect on antibiotic use), the results presented in the Cochrane review don't appear to be particularly different to the inputs used for TA168, and hence it is considered unlikely that this would significantly alter the conclusions.
- Furthermore, excluding complications only made a difference when combined with changes to other assumptions (e.g. QoL) in the model used for TA168. In these combined scenarios, the ICER increased to >£30k in the 'otherwise healthy' population (see Tables 7.30 and 7.31 page 193 of the Assessment Group report). Importantly, these scenarios remained below £30k in the at-risk populations. These scenarios were discussed in full by the committee and their position (i.e. complications less plausible for otherwise healthy adults) is stated in paragraphs 4.3.13 - 4.3.16 of the FAD.
- Finally, the Cochrane review reports an increase in adverse events of a neuropsychiatric nature in the trials for oseltamivir in adults. The Cochrane review reports that: 'in prophylaxis trials of oseltamivir there was a significant increase in patients with psychiatric adverse events over the on- and off-treatment periods (RR 1.80, 95%CI 1.05 to 3.08, I2 statistic = 0%; RD 1.06%, 95%CI 0.07 to 2.76; NNT_H = 94, 95% CI 36 to 1538)'. Such a result was not reported for the treatment trials of oseltamivir or for any of the trials with zanamivir. Although this is important new data, and potentially could be relevant to be considered in a technology appraisal, we consider it first and foremost something for the regulators to look at.
- Second, it is unclear what the signal for these adverse events is in the group of interest in TA158 – 'at risk patients' – as the Cochrane review only reports of 'healthy adults' in this respect.
- Third, even if this signal is exactly replicated in the at risk group, with the same intensity, and the same distribution over the various psychiatric conditions, it is difficult to be certain about the impact on the cost effectiveness of the drugs without performing the analyses. The signal is low for oseltamivir (2.20%), representing 44 events in 2000 subjects, compared with a comparably low signal for placebo (1.32% - 19 events in 1434 subjects), leading to a small difference; 0.88% in favour of placebo. Finally, it is not clear what level of severity of depression - the main event in this category – was reported for patients in these trials, although it is reported by Cochrane that of the 66 events in this category, 12 were classified as 'severe intensity' (10 oseltamivir, 2 placebo)..

Again, three respondents agreed with the proposal to move the guidance to the static list. Two respondents provided 'no comment', and the Cochrane Acute Respiratory Infections Group disagreed.

On balance, NICE has come to the view that the guidance does not, at this stage, need reviewing.

2. Summary of consultee and commentator responses

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

<p>Respondent: Alliance Pharmaceuticals</p> <p>Response to proposal: Agree</p> <p>Alliance agree to the proposal to move the guidance to the static list.</p>	<p>Comment from Technology Appraisals</p> <p>Comment noted. No action required.</p>
<p>Respondent: Roche Products</p> <p>Response to proposal: Agree</p> <p>Roche Products Limited supports the Institute's proposed approach that TA158 (Oseltamivir, amantadine and zanamivir for the prophylaxis of influenza) remains on the static list, and TA168 (Amantadine, oseltamivir and zanamivir for the treatment of influenza) should be added to the static list as originally proposed.</p>	<p>Comment from Technology Appraisals</p> <p>Comment noted. No action required.</p>
<p>Respondent: GlaxoSmithKline</p> <p>Response to proposal: Agree</p> <p>GlaxoSmithKline agree to the proposal that TA158 should remain on the static list and TA168 should be added to the static list. There is no new evidence for zanamivir that we are aware of that would affect this proposal.</p>	<p>Comment from Technology Appraisals</p> <p>Comment noted. No action required.</p>

<p>Respondent: Healthcare Improvement Scotland</p> <p>Response to proposal: No comment</p> <p>Healthcare Improvement Scotland has no comment to make on the proposal to move these appraisals to the static list.</p>	<p>Comment from Technology Appraisals</p> <p>Comment noted. No action required.</p>
<p>Respondent: Association of Renal Technologists</p> <p>Response to proposal: No comment</p> <p>The Association of Renal Technologists is not involved in this technology so will not be offering a response.</p>	<p>Comment from Technology Appraisals</p> <p>Comment noted. No action required.</p>
<p>Respondent: Medicines and Healthcare Products Regulatory Agency</p> <p>Response to proposal: No comment</p> <p>The view of the MHRA on the Cochrane review analysis of oseltamivir was in accordance with that of the European Medicines Agency (EMA), that is, that it provided no new evidence to alter the known balance of risks and benefits of oseltamivir for its authorised use, and had no regulatory implications. The clinical trials included in the review had already been evaluated by regulators.</p> <p>On this basis, MHRA had no comments or additional contribution to make to the NICE consultation as the proposal was consistent with the regulatory position.</p>	<p>Comment from Technology Appraisals</p> <p>Comment noted. No action required.</p>
<p>Respondent: Cochrane Acute Respiratory Infections Group</p> <p>Response to proposal: See below</p>	<p>Comment from Technology Appraisals</p> <p>See below</p>

Issue 1: Healthy or 'at risk' population

- NICE response to 2014 Cochrane review
 - The population for whom oseltamivir and zanamivir are recommended by NICE is the 'at-risk' group as defined in TA158 and 168. The Cochrane update reports on evidence for healthy adults and children, without providing results for subgroups, including what could be considered as the 'at-risk' population.
- Cochrane comment on NICE's response
 - The NICE commentary's statement that the Cochrane review only reports "on evidence for healthy adults and children, without providing results for subgroups, including what could be considered as the 'at-risk' population" is wrong.
 - This error is understandable because of the title of the review (which uses the word 'healthy' to separate out other seriously ill subpopulations that may be addressed in different Cochrane reviews). But our review did not exclude "at-risk populations". Our inclusion criteria state (our emphasis): "We included previously healthy people (children and adults). 'Previously healthy' includes people with chronic illness (such as asthma, diabetes, hypertension) but excluding illnesses affecting the immune response (such as cancer and AIDS). We included only trials on people exposed to naturally occurring influenza with or without symptoms. We targeted the intention-to-treat (ITT) and safety populations as our prior review discovered compelling evidence that the ITTI populations (the sub-population deemed to be influenza infected) were not balanced between treatment groups in the Roche oseltamivir trials. In addition, estimates from the ITT population will be more generalisable to clinical practice where routine testing for influenza is not common in many countries (and even where used, remains of variable accuracy)". (see p6 of our Cochrane review report)
 - In our review, 5 trials included adults with at least one of these complications, and 3 trials included children with asthma. Subgroup analyses were carried out whenever we observed heterogeneity of results in the ITT population. This happened only once in children (Analysis 1.46), which led us to do a subgroup analysis of asthmatic children (no evidence of effect – see also point 2). In all other possible subgroups the ITT results did not suggest heterogeneity of treatment effect, so our findings apply to all subpopulations studied which, again, included those NICE considers "at-risk". However you should note that the evidence shows that oseltamivir is less effective in populations with co-morbidities.
- NICE response to Cochrane's comment

- There are broadly two reasons to investigate 'subgroups'; likelihood of differential effectiveness between the groups, and/or evidence of differential 'risk' of key (health economic) outcomes. The former would have been of interest to Cochrane, while the latter is one that is mostly of interest to those that assess cost-effectiveness.
- The Assessment Group for TA168 assumed that both are in play: *'The distinction between otherwise healthy subjects and at-risk subjects, in terms of the alternative age groupings, are principally driven by the different underlying baseline rates of complication and mortality and the remaining life expectancy associated with these different populations. However, differences between otherwise healthy adults, otherwise healthy children and at-risk groups (as a whole) are also informed by subgroup specific estimates of the relative effectiveness of each NI in terms of symptom duration and reductions in complications (proxied by the reduction in antibiotic use).'* HTA monograph page 106 [Burch J, et al. Health Technol Assess 2009; 13(58)].
- We acknowledge that the different clinical effectiveness reviews come to slightly different conclusions in terms of the difference in effect size for the different outcomes when the 'at risk' population is compared with the 'otherwise healthy' population. That was the case at the time of consideration of the evidence for the development of NICE guidance, and remains the case now.
- The conclusions of the Assessment Group at the time of the production of guidance are clear: For the at-risk subgroups, effect sizes for differences in symptom duration were generally larger, and potentially more clinically significant, than those seen in healthy adults. However, there was greater uncertainty around these results, with estimates often failing to reach statistical significance. For the overall at-risk population, treatment reduced the median duration of symptoms by approximately 1–2 days with zanamivir, and by 0.50–0.75 days with oseltamivir. A similar pattern was seen in the time taken to return to normal activity, with the median reduction being between 1 and 2 days with zanamivir and 0.75 and 2.50 (data for at-risk adults only) days with oseltamivir. HTA monograph page xi [Burch J, et al. Health Technol Assess 2009; 13(58)].
- Overall, oseltamivir reduced the median time to alleviation of symptoms by 0.68 days (95% confidence interval [CI] 0.41 to 0.95) and 0.95 days (95% CI 0.50 to 1.39) in the ITT (n = 5036) and ITTI (n = 2541) analyses, respectively. The reduction in median time to alleviation of symptoms associated with oseltamivir treatment ranged from 0.41 days (older people) to 0.88 days (healthy and 'at-risk' children) in the ITT analyses and from 0.43 days ('at-risk' children) to 1.50 days (healthy children) in the ITTI analyses. [TA168 para 4.1.5]
- Overall, oseltamivir reduced the median time to return to normal activity by 1.32 days (95% CI 0.91 to 1.73) and 1.51 days (95% CI 1.01 to 2.02) in the ITT (n = 2754) and ITTI (n = 3013) analyses, respectively. The reduction in median time to

return to normal activity associated with oseltamivir treatment ranged from 1.25 days (healthy children) to 4.09 days (older people) in the ITT analyses and from 0.50 days ('at-risk' children) to 3.07 days (older people) in the ITTI analyses [TA168 para 4.1.6].

Issue 2: effectiveness in 'at risk' population

- NICE response to 2014 Cochrane review
 - The Committee noted that in all of the population subgroups, treatment with either antiviral drug was associated with reductions in the average duration of symptoms compared with placebo, although the difference was not statistically significant in all subgroups. The Committee acknowledged that the reduction in duration of symptoms was generally greater for the 'at-risk' population compared with healthy populations.
 - Although the effect sizes in terms of symptomatic benefits are perhaps a little lower than was assumed in the analyses performed for NICE in TA168, they are not inconsistent with the range of estimates applied in different scenarios explored for that guidance. In those scenarios more conservative symptomatic benefits (which appear comparable to those reported here) were applied, resulting in oseltamivir as still being cost-effective. [HTA monograph page [Burch J, et al. Health Technol Assess 2009; 13(58)]. Scenario 3 p123 and Table 82, Scenario 12 p131-133, Tables 94-95. These scenarios explored different symptom definitions and best/worst case scenarios for symptom outcomes. Results robust to smaller effect differences in symptom duration compared to base-case.]
- Cochrane comment on NICE's response
 - The NICE commentary's states "The Committee acknowledged that the reduction in duration of symptoms was generally greater for the 'at-risk' population compared with healthy populations." This statement needs to be referenced: we cannot trace the evidence on which it is based.
 - The evidence from clinical study reports in our review is contrary. For oseltamivir, 5 adult treatment trials focused on at-risk groups (3 in the elderly and 2 in patients with COAD). For these trials, the treatment effect for time to first alleviation of symptoms was 8.4 hours reduction in TF group (95% CI: -25.4 to 8.7 hours; P=0.34, I2 = 0%). Therefore the reduction in duration of symptoms was generally lower for the at-risk population. (The general population effect was a 16.8 hours reduction (95% CI: 8.4 to 25.1 hours, P<0.001, I2 = 0%).

- For oseltamivir treatment of children, 3 trials were in children with asthma. For these trials the treatment effect for time to first alleviation of symptoms was 5.2 hours increase in TF group (95% CI: -11.1 to 21.4; P=0.53, I² = 0%).(p19) Once again, the evidence shows that the drug was less effective in the “at-risk” population.
- NICE response to Cochrane’s comment
 - The statement by Committee is from the FAD section 4.3.5, and in particular: ‘The Committee heard from clinical experts that this increased reduction in duration of symptoms for the ‘at-risk’ group was plausible for a number of reasons. It is likely that people in ‘at-risk’ groups would have a longer duration of illness, and would therefore be more likely to benefit from antiviral treatment. There is also clinical rationale to suggest that people in ‘at-risk’ groups could also suffer from exacerbations of underlying conditions as a result of influenza. This could increase the duration and severity of influenza symptoms, which would mean an increased potential benefit from antiviral treatments. These exacerbations might also lead to a person not recovering completely, and future influenza infections and subsequent exacerbations being more frequent. The Committee concluded that there is evidence indicating clinical effectiveness of antiviral drugs in a wide range of clinical settings, but that their use is of greatest clinical importance for people in ‘at-risk’ groups.’
 - The supporting evidence is found in FAD sections 4.1.5 and 4.1.6 for oseltamivir (see above), and 4.1.10 and 4.1.11 for zanamivir, as well as the HTA monograph by the Assessment Group: ‘When compared with placebo, zanamivir reduced the median duration of symptoms by between approximately 0.5 and 1 days, and oseltamivir by between 0.5 and 1.5 days in healthy adults. The median reduction in the time taken to return to normal activity was about 0.5 days with zanamivir and 1.5–2.5 days with oseltamivir. Although these results were statistically significant, the absolute effects were small and their clinical significance in an otherwise healthy population questionable. For the at-risk subgroups, effect sizes for differences in symptom duration were generally larger, and potentially more clinically significant, than those seen in healthy adults. However, there was greater uncertainty around these results with estimates often failing to reach statistical significance, although the direction of effect remained in favour of treatment with Nis. For the overall at-risk population, treatment reduced the median duration of symptoms by approximately 1–2 days with zanamivir, and by 0.5–0.75 days with oseltamivir. A similar pattern was seen in the time taken to return to normal activity, with the median time being between 1 and 2 days with zanamivir and 0.75 and 2.5 (data for at-risk adults only) days with oseltamivir.’ HTA monograph page 139 [Burch J, et al. Health Technol Assess 2009; 13(58)].
 - In general, the ICER estimates were lower (and hence more favourable) in at-risk populations than in otherwise healthy populations. This finding partly reflects the inclusion of potential benefits attributed to reductions in hospitalisation and mortality and the higher underlying baseline rates of these events in at-risk populations. However, it is also worth noting that

differences in mean symptom duration were also assumed to be larger for at-risk populations than those for healthy populations, based on the results from the Bayesian synthesis of symptom data (with the highest gains estimated for zanamivir). HTA monograph page 132 [Burch J, et al. Health Technol Assess 2009; 13(58)].

Issue 3: complications of influenza

- NICE response to 2014 Cochrane review
 - Although it is more difficult to compare inputs for complications given the different definitions employed in the Cochrane paper and the approach used in the economic model for TA168 (i.e. linking all complications via treatment effect on antibiotic use), the results presented in the Cochrane review don't appear to be particularly different to the inputs used for TA168, and hence it is considered unlikely that this would significantly alter the conclusions. Furthermore, excluding complications only made a difference when combined with changes to other assumptions (e.g. QoL) in the model used for TA168. In these combined scenarios, the ICER increased to >£30k in the 'otherwise healthy' population (see Tables 7.30 and 7.31 page 193 of the Assessment Group report).
 - Importantly, these scenarios remained below £30k in the at-risk populations. These scenarios were discussed in full by the committee and their position (i.e. complications less plausible for otherwise healthy adults) is stated in paragraphs 4.3.13 - 4.3.16 of the FAD.
- Cochrane comment on NICE's response
 - No specific comments received on statements in proposal paper
- NICE response to Cochrane's comment
 - As per the first response.

Issue 4: adverse effects and harms of treatment

- NICE response to 2014 Cochrane review

- The Cochrane review reports an increase in adverse events of a neuropsychiatric nature in the trials for oseltamivir in adults. The Cochrane review reports that: ‘in prophylaxis trials of oseltamivir there was a significant increase in patients with psychiatric adverse events over the on- and off-treatment periods (RR 1.80, 95%CI 1.05 to 3.08, I2 statistic = 0%; RD 1.06%, 95%CI 0.07 to 2.76; NNT_H = 94, 95% CI 36 to 1538)’. Such a result was not reported for the treatment trials of oseltamivir or for any of the trials with zanamivir. Although this is important new data, and potentially could be relevant to be considered in a technology appraisal, we consider it first and foremost something for the regulators to look at.
- Second, it is unclear what the signal for these adverse events is in the group of interest in TA158 - at risk patients - as the Cochrane review only reports on ‘healthy adults’ in this respect.
- Third, even if this signal is exactly replicated in the at risk group, with the same intensity, and the same distribution over the various psychiatric conditions, it is difficult to be certain about the impact on the cost effectiveness of the drugs without performing the analyses. The signal is low for oseltamivir (2.20%), representing 44 events in 2000 subjects, compared with a comparably low signal for placebo (1.32% - 19 events in 1434 subjects), leading to a small difference; 0.88% in favour of placebo. Finally, it is not clear what level of severity of depression - the main event in this category - was reported for patients in these trials, although it is reported by Cochrane that of the 66 events in this category, 12 were classified as ‘severe intensity’ (10 oseltamivir, 2 placebo).
- Cochrane comment on NICE’s response
 - **Harms**
 - Neuropsychiatric adverse effects. The NICE commentary includes a discussion of neuropsychiatric adverse effects but say “such a result was not reported for the treatment trials of oseltamivir”. There was no evidence that psychiatric events in oseltamivir groups in treatment trials increased overall. However, we found dose response-significant increase of psychiatric adverse events in the two oseltamivir “pivotal” treatment trials, WV15670 and WV15671, at 150 mg (standard dose) and 300 mg daily (high dose) (P = 0.038) (p2, p25). There was no indication of a dose-response effect of treatment on psychiatric adverse events in the only prophylaxis study with multiple dose treatment groups (WV15673/WV15697). Moreover we discussed the reasons why oseltamivir treatment trials may have failed to identify a clear association between oseltamivir and psychiatric harms (p38). It is possible that influenza-like illness and influenza symptoms masked the harms in those who were already symptomatic and therefore recruited in the treatment trials. In addition common influenza-type symptoms were excluded from reporting as adverse events in the

treatment trials. Prospective and intentional collection of psychiatric events with several thousand participants may be necessary in treatment RCTs (p38).

- Other adverse effects: The NICE commentary only includes a discussion of the psychiatric adverse events our review found (the NICE commentary erroneously labels them neuropsychiatric). However the NICE commentary omits discussion of our findings of increased risk of renal events, and the evidence of hyperglycaemia associated with oseltamivir for prophylaxis (p3, p26). In prophylaxis trials, there were four deaths in total, all in elderly patients, with two in the placebo group and two in the oseltamivir group. Causes of death were reported as two cancers, one myocardial infarction and one intestinal perforation. However, for both deaths in the oseltamivir arms the participants experienced acute renal failure on-treatment prior to death (p27). We also discussed renal adverse effects on p37 of our review. This may be important because NICE guidelines recommend oseltamivir for a number of subpopulations deemed “at risk” which include people with renal disorders, but they do not discuss renal harms that may be induced by the drug. It is important that NICE considers and perhaps communicates these data – the number needed to harm for renal adverse events was as few as one per 150 patients treated, and the result for renal events was statistically significant ($P=0.02$) in a sensitivity analysis. (p26 with Figure 11). We also identified eight cases of metabolic disturbance (hyperglycaemia or exacerbation of diabetes) out of 2000 recipients of oseltamivir in five prophylaxis trials compared with no cases in 1434 recipients of placebo (p37-38). Given the low numbers, we did not meta-analyse the data (as stated in our protocol), but a rate of 4 per 1000 is high enough to raise concerns. If oseltamivir is recommended to diabetic patients because of “high risk”, oseltamivir may worsen the disease. We noticed that oseltamivir significantly increased the proportion of patients with prolonged QTc intervals (NNT_H 25) (p25). QTc prolongation is closely related to the concentration of oseltamivir carboxylate in the animal experiments done by Roche. If oseltamivir is recommended to patients with cardiac failure or other conditions prone to induce arrhythmia because of “high risk”, it may induce QTc prolongation and may induce fatal arrhythmia. We have explained that because of the confounding in the Roche-funded trials of complications with adverse effects (what we term “compliharms” in a compound word to embrace both meanings) we cannot rule out that these harms are present in treatment as well prophylaxis trials. For zanamivir, we found no significant effect on otitis media or sinusitis in both adults and children, and the only small effect noted was for bronchitis in adults, a condition that is treated conservatively in general practice.

- **Mechanisms underlying lack of efficacy and harm**

- The NICE document omits any mention of the effect of oseltamivir on reducing influenza antibody production that we reported in our review, seen primarily in treatment trials. It is a very important finding that questions the very nature of the mechanism of action of oseltamivir. This was consistent with the evidence from animal tests. (p36).
 - Reduction of influenza symptoms does not appear to be related to viral reduction. There is also evidence for this in the findings that administration of oseltamivir in animals challenged by respiratory syncytial virus (RSV) lacking a neuraminidase gene showed a symptom-relieving effect. We discussed this at p36. You should note that this interpretation is consistent with the evidence of the mode of action of oseltamivir from animal models from the pharmaceutical company (Module 2, Background and Rationale in the protocol of WV15670; WV15671) (p36).
 - Reduction of influenza symptoms in zanamivir trials may not be related to viral reduction either. We noted that inhaled zanamivir could reach a high enough concentration to reduce the immune response if it is administered at a high dose or for a long period, or if the patient is very susceptible (p36). In the zanamivir treatment trials we compared effects on time to first symptom relief and there was no evidence of difference between infected and non-infected patients. We could not do this analysis for oseltamivir trials as influenza infection was misclassified due to oseltamivir's suppression of antibody response, so there appears to be no valid way to determine who had influenza and who had non influenza influenza-like illness.
- **Evidence of harm other than the results from systematic review**
 - We are also concerned that the NICE document does not address the evidence from other studies such as prospective cohort studies and animal toxicity studies that we discuss in our review (p38). These studies suggest a causal relationship between neuropsychiatric adverse effects and oseltamivir. A single prospective cohort study with nearly 10,000 participants and meta-analysis of three such studies including this showed increased incidence of delirium, unconsciousness and/or abnormal behaviour (p38).
- NICE response to Cochrane comment
 - In TA158 and 168, where the technologies are described, reference is made to the potential for 'psychiatric side effects', amongst others, and therefore reference to it has already been made (in view of the request for further action from NICE): TA158 - 3.2 Adverse effects associated with oseltamivir include gastrointestinal symptoms, bronchitis and cough, dizziness and fatigue and neurological symptoms such as headache, insomnia and vertigo. Skin rashes and allergic reactions and, rarely, hepatobiliary system disorders have been reported. Convulsions and psychiatric events, mainly in children and

adolescents, have also been reported but a causal link has not been established. For full details of adverse effects and contraindications, see the summary of product characteristics (SPC). TA168 - 3.5 Adverse effects associated with oseltamivir include gastrointestinal symptoms, bronchitis and cough, dizziness and fatigue and neurological symptoms such as headache, insomnia and vertigo. Skin rashes and allergic reactions and, rarely, disorders of the hepatobiliary system have been reported. Convulsions and neuropsychiatric disorders, mainly in children and adolescents, have also been reported but a causal link has not been established. For full details of adverse effects and contraindications, see the SPC.

- Furthermore, TA158 acknowledges that Committee considered this issue in more detail, and noted that data is available from trials in other countries, but that no specific guidance has been received from the MHRA: 4.3.7 The Committee accepted that the neuraminidase inhibitors were generally safe and well tolerated. It was aware of concerns that have been raised with regulatory authorities in Canada, Japan and the USA about possible neuropsychiatric events associated with oseltamivir in adolescents, but that no specific guidance regarding safety has been issued by the European Medicines Agency or the Medicines and Healthcare products Regulatory Agency. The Committee accepted that amantadine was associated with more frequent adverse effects. The Committee also accepted evidence of viral resistance to amantadine, and noted that there was also evidence of increasing resistance to the neuraminidase inhibitors although it was currently low.
- From Stephen Palmer, co-author of the HTA monograph [Burch J, et al. Health Technol Assess 2009; 13(58)] that informed TA168 – treatment guidance:
 - The problem with trying to separate the argument into issues related to complications and those related to AEs is that there's obvious potential overlap. Hence, many of the events which you list under adverse events are also potential complications associated with influenza (or at least the events which may subsequently manifest themselves). The issue is then separating out the drug specific harms for these vs the potential benefits that may arise assuming a relationship between symptom duration/severity reduction and lower disease related complications. As long as you're happy that the overall balance of these remains positive (or at worst neutral) in the groups where treatment is approved (which seems to be the line EMA are taking more broadly), then I think your argument is fine.
 - The potential problem is that the scenarios we modelled allowed for either a positive effect (on average) on complications, or no effect. We didn't consider scenarios assuming that the risks (i.e. complications/AEs) might be higher (on average). However, I'm not sure why we should! It might be important to note that the treatment effects (see Table 72 p117) we applied to complications were uncertain and for some groups (e.g. lower risk populations) included the potential for the drug to increase complication rates. This uncertainty was fully reflected in the

subsequent scenarios e.g. some of the simulations would have included results where the complication rate was higher on treatment compared to placebo. However, on average, the results showed not only an acceptable risk/benefit balance but also an acceptable cost-effectiveness, particularly for the higher risk groups.

- There's another interesting point which you might want to consider from Table 72. In general, the estimates we applied to higher risk populations for complications were more precise than lower risk groups and also didn't include 1 in some of the subgroups. Clearly some of this might just be due to precision (i.e. different sample sizes) but clearly there's an issue about generalising the results from Cochrane which is largely driven by the findings from healthy populations to the higher risk populations within your recommendations. Given the overlap between complications/AEs it is difficult to separate out drug specific harms vs indirect benefits in the same outcome which might be achieved by shorter illness durations (or less severe episodes more generally). The reason that the 'signal' is potentially higher in lower risk groups is that there's less confounding or potential for offsetting the drug specific harm with the indirect benefits, because of the the much lower rate in which these complications occur in otherwise healthy patients. Clearly you can't ignore the potential signal but I'm not sure you can assume the same implications arise. If you believe (as the committee did) that there's a plausible relationship between symptom duration/severity and the incidence of complications, then the question becomes a balance between the drug specific harms vs. the reduction in complications which might be achieved through better symptom control. Hence, the lack of a similar signal in higher risk populations may just be that these risks are being offset by other effects on symptoms, particularly given the much higher underlying complication rates which are associated with influenza in these groups.
- I agree that you can't authoritatively state that these findings would have no impact on the ICER. However, I think its reasonable to conclude that the likelihood that they could alter the current recommendations is probably nil. As long as the EMA continue to determine that the overall risk /benefit balance is positive then I really don't see the cost-effectiveness in currently recommended populations being an issue. More importantly, given the difficulty in disentangle complications from AEs and drug specific harms vs illness duration benefits, I can't see an easy way of modelling this to get an authoritative answer and the prospect of spending significant sums to demonstrate this would seem better spent elsewhere.
- 'When data were available for adverse events and complication rates, there was little overall difference associated with the use of either zanamivir or oseltamivir when compared individually with placebo. However, data were reported for few trials, studies were not designed to detect changes in these outcomes, and the numbers of events were generally very small. The most consistent data and strongest evidence related to antibiotic use, with both zanamivir and oseltamivir resulting in

statistically significant reductions in antibiotic use'. HTA monograph page xi [Burch J, et al. Health Technol Assess 2009; 13(58)].

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