1 Executive Summary

1.1 Background

The National Institute for Health and Clinical Excellence (NICE) is conducting a review of the Institute's earlier advice on the clinical and cost-effectiveness of amantadine and oseltamivir[1], and to advise on the clinical and cost-effectiveness of zanamivir, in their licensed indications for the prevention of influenza A and B, both relative to one another and to best symptomatic care.

Additional systematic searches of the literature were carried out to identify recently published evidence on the safety and effectiveness of neuraminidase inhibitors for influenza prophylaxis since the publication of the recent 2006/7 Cochrane reviews and the Canadian HTA. As a result of the literature searches' new clinical studies, reviews, and meta-analyses were identified that were not included at the time of the original NICE appraisal[1]. Furthermore, extensions to the existing licence of oseltamivir have occurred since the original technology appraisal.

Consequently updated estimates of the cost effectiveness of oseltamivir for the post-exposure and seasonal prophylaxis of patients have been estimated across all relevant patient groups. The following evidence provided by Roche indicates that household post exposure prophylaxis of healthy adults can be considered a cost effective use of NHS resources and the existing guidance for "at risk" patients only may no longer be appropriate given the new evidence.

1.2 Antiviral Prevention of Influenza

1.2.1 Neuraminidase inhibitors

Oseltamivir (Tamiflu®) is the only licensed orally active neuraminidase inhibitor for the treatment and prevention of influenza. It is a pro-drug of the active metabolite oseltamivir carboxylate, which is produced by hydrolysis of oseltamivir phosphate in the liver.

Oseltamivir is licensed for treatment and prophylaxis of influenza in individuals one year or older. Treatment is given when patients present within 48 hours of the onset of the symptoms of influenza. Post exposure prophylaxis is administered within 48 hours of suspected contact with an influenza index case for up to 10 days and seasonal prophylaxis may be given daily when influenza is circulating to prevent infection for up to 6 weeks.

Zanamivir (Relenza) is a neuraminidase inhibitor. Zanamivir is administered via inhalation as a dry powder via a device known as the 'Diskhaler.' The loading, priming and inhalation of the drug are part of a multi-step process.

- Neuraminidase inhibitors target the highly conserved target of the viral neuraminidase enzyme
- Neuraminidase inhibitors are active against influenza A and B
- Tamiflu is the only orally administered neuraminidase inhibitors available with Relenza being administered through an inhaler

- As Tamiflu is orally administered, its action is systemic – which has significance in certain strains of influenza such as H5N1
- Through inhalation, Relenza has a topical, local action on influenza in the lungs and does not have a systemic action
- The use of inhalers in the case of severe influenza is problematic – furthermore the Diskhaler device utilised for Relenza is not as easy to deploy as an oral product

1.3 The Clinical Effectiveness of Oseltamivir for Influenza Prophylaxis

As a result of the literature searches new clinical studies, reviews, and meta-analyses were identified that were not included in the original NICE appraisal. In particular, the following references are included in this submission:

Management of influenza in households:
Hayden FG, Belshe R, Villanueva C, Lanno R, Hughes C, Small I, Dutkowski R, Ward P, Carr J. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. J Infect Dis. 2004; 189(3): 440-9.

Antiviral effects on influenza viral transmission and pathogenicity:
Halloran ME, Hayden FG, Yang Y, Logini IM, Monto S. Antiviral Effects on Influenza Viral Transmission and Pathogenicity: Observations from Household-based Trials. Am J Epidemiol 2007; 165: 212-221

Prevention of influenza outbreaks in an unvaccinated long-term care population:
Ambrozaitis A, Gravenstein S, van Essen GA, Rubinstein E, Balciuniene L, Stikleryte A, Crawford C, Elliott M, Shult P. Inhaled zanamivir versus placebo for the prevention of influenza outbreaks in an unvaccinated long-term care population. J Am Med Dir Assoc. 2005; 6(6): 367-74.

Control of influenza in a highly vaccinated long-term care population:
Gravenstein S, Drinka P, Osterweil D, Schilling M, Krause P, Elliott M, Shult P, Ambrozaitis A, Kandel R, Binder E, Hammond J, McElhaney J, Flack N, Daly J, Keene O. Inhaled zanamivir versus rimantadine for the control of influenza in a highly vaccinated long-term care population. J Am Med Dir Assoc. 2005 Nov-Dec;6(6):359-66.

Prevention of influenza in community-dwelling, high-risk adult and adolescent subjects:
LaForce C, Man CY, Henderson FW, et al. Efficacy and Safety of Inhaled Zanamivir in the Prevention of Influenza in Community-Dwelling, High-Risk Adult and Adolescent Subjects: A 28-Day, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Clinical Therapeutics 2007; 29(8): 1579-1590.

Influenza virus susceptibility and resistance to oseltamivir
Aoki F.Y., Boivin G., Roberts N. Influenza virus susceptibility and resistance to oseltamivir. Antiviral therapy 2007; 12: 603-616.

1.3.1 *Neuraminidase inhibitor studies of post-exposure prophylaxis (PEP) of influenza in the household setting*

Four clinical studies were identified investigating PEP of influenza in the household setting. Three of the studies: zanamivir (Hayden et al., 2000 and Monto et al., 2002) and oseltamivir (Welliver et al., 2001) are double-blind, placebo control trials, whereas oseltamivir (Hayden et al., 2004) is an open label study. In the oseltamivir (Hayden et al., 2004) study, PEP was compared against treatment upon development of influenza-like illness during the post-exposure period. In the other three studies PEP was compared against placebo.

As earlier use of neuraminidase inhibitors is already known to impact positively on treatment outcomes timing of administration is particularly important.
For example, in the two zanamivir trials, study medication was administered within 36 hours of onset of influenza-like symptoms, whereas this was within 48 hours of onset of influenza-like symptoms in the oseltamivir studies.

In the analysis of paediatric influenza prevention, only the oseltamivir study (Hayden et al., 2004) investigated post-exposure prophylaxis of influenza in very young patients (≥1 year) and reported outcomes in those aged 1-12 years. In the two zanamivir studies (Hayden et al., 2000 and Monto et al., 2002) paediatric patients (≥5 years) were investigated but no reported outcomes were given for the paediatric patients.

The index cases were not treated in two studies oseltamivir (Welliver et al., 2001). and zanamivir (Monto et al., 2002). In the oseltamivir (Hayden et al., 2004) study all index cases were treated with oseltamivir. In the zanamivir (Hayden et al., 2000) study index cases were randomised to treatment with zanamivir or placebo.

The duration of PEP was 10 days in three of the studies: zanamivir (Hayden et al., 2000 and Monto et al., 2002) and oseltamivir (Hayden et al., 2004), but only 7 days in the oseltamivir (Welliver et al., 2001) study.

Protective efficacy against symptomatic laboratory confirmed influenza was high in all four studies. For the ITT household population:

oseltamivir (Welliver et al., 2001)	86% (95% CI 60-95%)
oseltamivir (Hayden et al., 2004)	63% (95% CI 26-81%)
zanamivir (Hayden et al., 2000)	79% (95% CI 57-89%)
zanamivir (Monto et al., 2002)	81% (95% CI 64-90%)

The 95% confidence intervals overlap, indicating comparable efficacy rates between the studies

Protective efficacy against symptomatic laboratory confirmed influenza in children was only reported for oseltamivir (Hayden et al., 2004). For the ITT individual contact paediatric population the protective efficacy of oseltamivir was 64% (95% CI 16-85%).

In all four studies PEP was generally well tolerated. There were fewer GI AEs in those who received oseltamivir once-daily PEP than those who received twice-daily treatment (Hayden et al., 2004).

Halloran et al. (2007) re-analysed the two household-based randomised trials each of zanamivir (Hayden et al., 2000 & Monto et al., 2002) and oseltamivir (Welliver et al., 2001 & Hayden et al., 2004) in order to estimate four discrete efficacy measures:

Standardised data from the original study reports were utilised to estimate pathogenicity, antiviral efficacy for pathogenicity, and the antiviral effect on infectiousness. Pathogenicity in controls ranged from 44% to 66%. Efficacy in reducing pathogenicity for zanamivir was 52% and 56% in the two studies; for oseltamivir, it was 56% and 79%. The effect on reducing infectiousness was 19% for zanamivir and 80% for oseltamivir. The authors speculated that oseltamivir's superior efficacy at reducing transmission may be due to the fact that inhaled zanamivir though effective at reducing cough, did not reduce nasal transmission of influenza.

- Neuraminidase inhibitor studies of post-exposure prophylaxis (PEP) of influenza in the household setting have shown clear effectiveness in 4 well designed studies with protective effectiveness ranging from 52 to 56% in Relenza studies and 56 to 79% in Tamiflu studies
- Only the oseltamivir study (Hayden et al., 2004) investigated post-exposure prophylaxis of influenza in very young patients (≥1 year) and reported outcomes in those aged 1-12 years.

1.3.2 Neuraminidase inhibitors in outbreak control of influenza in long-term care facilities

Vaccination is the mainstay of seasonal influenza prevention. In exceptional circumstances, seasonal prophylaxis with antiviral agents may be considered to avert the transmission of influenza. There are a number of published studies which examine the efficacy of neuraminidase inhibitors in this setting. Seasonal prophylaxis may be particularly useful in exceptional circumstances. For example as discussed previously, if there is a vaccine mismatch situation or in the management of an institutional outbreak such intervention would be warranted. It should be noted however, that in the management of outbreaks in elderly institutions for example, logistical issues such as the need for tutoring and demonstration of inhaler technique and the necessity for a separate inhaler for each patient to avoid cross-contamination could prove cumbersome. As oseltamivir is an oral therapy this issue does not arise.

Bowles et al reported a descriptive case series examining the use of oseltamivir for treatment and prophylaxis of influenza outbreaks in long term care facilities. These results demonstrated a particularly positive effect on the reduction of serious complications, hospitalisations, antibiotic use and death. Neither of the two zanamivir studies: (Gravenstein et al., 2005 and Ambrozaitis et al., 2005) found a statistically significant reduction in influenza-related complications in patients with laboratory confirmed influenza. Zanamivir (Gravenstein et al., 2005) was standard of care controlled, whereas zanamivir (Ambrozaitis et al., 2005) was placebo-controlled.

Both zanamivir and oseltamivir prophylaxis therapies were well tolerated. No evidence of resistance to zanamivir or oseltamivir was found before or after treatment prophylaxis, including prophylaxis failure. This is in contrast to rimantadine, to which resistance was prevalent (38% of isolates) (zanamivir (Gravenstein et al., 2005 study).

- Long term care facilities are clearly indicated as an important target to reduce influenza spread to the broader community and furthermore, by definition, involve patients who are considered a risk group due to their immunocompromised nature, prophylaxis in this setting with neuraminidase inhibitors should be considered
- Neuraminidase inhibitors have been studied for outbreak control of influenza in long-term care facilities
- In a large multicentre case series, prophylaxis oseltamivir showed a statistically significant reduction of serious complications, hospitalisations, antibiotic use and death.

1.3.3 Neuraminidase inhibitors in seasonal influenza prophylaxis of healthy adults, adults and adolescents at high risk for complications of influenza and a vaccinated frail older population

Four randomised, double-blind placebo-controlled trials were carried out to investigative the protective efficacy of neuraminidase inhibitors in seasonal influenza: Oral oseltamivir (Hayden et al., 1999 & Peters et al., 2001) and inhaled zanamivir (Monto et al., 1999 & LaForce et al., 2007). Two of the studies were in healthy adults: oral oseltamivir (Hayden et al., 1999) and inhaled zanamivir (Monto et al., 1999), .One was in vaccinated frail elderly subjects: oral oseltamivir (Peters et al., 2001) and ne was in adults and adolescents at high risk for complications of influenza (LaForce et al., 2007).

The oral oseltamivir (Hayden et al., 1999 & Peters et al., 2001) studies involved prophylaxis for 6 weeks whereas the Inhaled zanamivir (Monto et al., 1999 & LaForce et al., 2007) studies involved prophylaxis for 4 weeks.

Protective efficacies (95% CI) for the once-daily treatment regimens against laboratory confirmed symptomatic influenza (ITT) were:

oral oseltamivir (Peters et al., 2001):	92% (p=0.002)
oral oseltamivir (Hayden et al., 1999):	76% (46-91%)
inhaled zanamivir (Monto et al., 1999):	67% (39-83%)
inhaled zanamivir (LaForce et al., 2007):	83% (56-93%)

Two studies reported protective efficacy against laboratory confirmed symptomatic influenza in vaccinated subjects:

oral oseltamivir (Peters et al., 2001):	91% (p=0.003)
inhaled zanamivir (LaForce et al., 2007):	0.1% vs. 0.5% (placebo)
	(% protective efficacy not estimated)

Two studies reported similar protective efficacy against complications of laboratory confirmed symptomatic influenza:

oral oseltamivir (Peters et al., 2001):	85% (p=0.037)
inhaled zanamivir (LaForce et al., 2007):	88% (27-98%)

Administration of neuraminidase inhibitors for 4-6 weeks during seasonal influenza was generally well tolerated.

There were no reports of the presence prior to or the emergence following seasonal prophylaxis of influenza viral resistance to the either oseltamivir or zanamivir, although viral susceptibility testing was only reported for the oral oseltamivir (Hayden et al., 1999) studies and for the inhaled zanamivir (LaForce et al., 2007). .

- Neuraminidase inhibitors have been studied in seasonal influenza prophylaxis of healthy adults, adults and adolescents at high risk for complications of influenza and a vaccinated frail older population.
- The protective use of neuraminidase inhibitors are clearly proven in this setting
- The protective efficacy reported for studies where Tamiflu was utilised ranged between 92 and 76% and reached statistical significance whereas, in the Relenza studies efficacy ranged from 67 to 83%

1.4 Influenza virus susceptibility and resistance to oseltamivir

As with all other anti-infectives, clinical use of oseltamivir at recommended doses for the treatment and prophylaxis of seasonal influenza is associated with a low incidence of resistance

Cumulative data from Roche-sponsored clinical trials, involving almost 2,000 oseltamivir-treated patients, indicate that the incidence of reduced susceptibility to oseltamivir is 0.32% in adults and 4.1% in children. If studies with suboptimal dosing are excluded from the body of literature, the incidence of oseltamivir resistance decreases to 0.3% (adults) and 1.2% (children).

To-date, the clinical significance of resistant variants appears modest in immuno-competent individuals, although further research is needed to establish the incidence and clinical consequences of antiviral resistance in immuno-compromised subjects.

Continued worldwide surveillance in collaboration with the World Health Organisation will determine whether resistance to the neuraminidase inhibitors becomes an issue in the future management of influenza.

- Tamiflu has been used widely throughout the globe with current exposure being : 48.8 million patients
- Relenza has, to date, had relatively limited usage
- The level of resistance expected for a neuraminidase inhibitor is likely to be associated with the level of global usage
- Despite large exposure to Tamiflu, the resistance levels remain low for Tamiflu. Within closely monitored clinical trials, Tamiflu resistance was found to be 0.32% in adults and 4.1% in children

1.5 Oseltamivir Safety Profile (From Tamiflu® summary of product characteristics)

Since launch over 48.8 million patients have received Tamiflu® (based on IMS prescription data).

Data from pooled clinical studies suggest that, the most frequently reported adverse events with the administration of oseltamivir were nausea and vomiting. These events occur less frequently in elderly populations and were usually mild and transient and generally occurred with first dosing. Effects may also be diminished if the drug is taken with food.

Following a recent review, the European Agency for the Evaluation of Medicinal Products (EMEA) and Committee for Medicinal Products for Human Use (CHMP) requested inclusion of wording in the precautions section for oseltamivir of the European label to include an observed increase of neuropsychiatric reports, mainly in Japan, in those patients being treated for influenza.

As clinical studies have already shown, patients not treated with oseltamivir experience delirium and other events as a natural course of the infection and its associated high fever. The changes in labelling are a precautionary measure to alert medical professionals, as well as parents and guardians, to closely monitor influenza patients for any signs of abnormal behaviour.

Reports of neuropsychiatric events in patients taking oseltamivir are rare relative to usage, and there is no established causal relationship between the use of oseltamivir and the likelihood of neuropsychiatric events in influenza patients. Furthermore, recently in Japan similar reports have occurred with zanamivir and amantadine pointing to an association with influenza like illness.

- The global exposure to Tamiflu is 48.8 million patients
- Neuraminidase inhibitors are generally well tolerated with leading adverse events being mild gastrointestinal upset, dermatitis, rash and eczema
- Neuropsychiatric events have been reported in the post-marketing surveillance of Tamiflu and are cited in its SmPC however no causal relationship has been allocated and this finding has remained rare. The neuropsychiatric events report were associated with peak pyrexic responses during the influenza infection

The adverse events considered at least possibly related to the treatment with zanamivir are listed below by body system, organ class and absolute frequency: Immune system disorders: allergic-type reaction including facial and oropharyngeal oedema (very rare); Respiratory, thoracic and mediastinal disorders: bronchospasm, dyspnea, throat tightness or constriction (very rare); Skin and subcutaneous tissue disorders: rash, urticaria (very rare).

- Both Amantadine and Relenza are generally well tolerated
- Amantadine unlike the neuraminidase inhibitors (oseltamivir and zanamivir) is contraindicated in individuals subject to convulsions; who have a history of gastric ulceration; who have severe renal disease; or who are pregnant.
- Bronchospasm has been reported in post-marketing surveillance of Relenza which may be acute or serious. Case histories of some subjects that experienced bronchospasm did not have a history of respiratory disease. It is postulated that this may be related to a direct irritant effect of zanamivir on the respiratory mucosa.

1.6 Cost Effectiveness Evidence

The economic model is a deterministic model based on a decision tree approach. The model allows for the cost effectiveness of oseltamivir compared to amantadine, zanamivir and usual care for post exposure and seasonal prophylaxis to be estimated.

This economic analysis takes into account four distinct patient populations which include otherwise healthy adults, otherwise healthy children 1-12 years, otherwise healthy children 1-5 years and at risk adults13-64 years with co-morbidities as well as all adults >64 years of age.

The design of the economic model is the same for all estimates however each estimate takes into account the respective clinical outcomes and associated costs for each population. The economic analysis for children aged 1-5 years will only look at oseltamivir compared to usual care, as the other anti-virals are not licensed in this age group. Consequently a total of 20 incremental cost effectiveness ratios (ICERs) will be reported reflecting the 2 methods of treatment, 3 potential comparators and 4 discrete age related sub groups of interest.

Results

Post exposure prophylaxis

Economic case		Incremental cost effectiveness ratio (ICER)
Otherwise healthy adults		
1.	Oseltamivir	£27,153
	Usual care	
2.	Oseltamivir	£2,141
	Amantadine	
3.	Oseltamivir	Oseltamivir is cost saving
	Zanamivir	
Otherwise healthy children 1-12 years		
4.	Oseltamivir	£7,977
	Usual care	
5.	Oseltamivir	Oseltamivir is therefore dominant.
	Amantadine	
6.	Oseltamivir	Oseltamivir is cost saving
	Zanamivir	
Otherwise healthy children 1-5 years		
7.	Oseltamivir	£5,610
	Usual care	
At risk adults		
8.	Oseltamivir	£1,983
	Usual care	
9.	Oseltamivir	£96
	Amantadine	
10.	Oseltamivir	Oseltamivir is cost saving
	Zanamivir	

Roche

Seasonal prophylaxis

Economic case		Incremental cost effectiveness ratio (ICER)
Otherwise healthy adults		
1.	Oseltamivir	£163,671
	Usual care	
2.	Oseltamivir	£237,055
	Amantadine	
3.	Oseltamivir	Oseltamivir and zanamivir are equivalent
	Zanamivir	
Otherwise healthy children 1-12 years		
4.	Oseltamivir	£90,551
	Usual care	
5.	Oseltamivir	£79,247
	Amantadine	
6.	Oseltamivir	Oseltamivir is cost saving
	Zanamivir	
Otherwise healthy children 1-5 years		
7.	Oseltamivir	£46,085
	Usual care	
At risk adults		
8.	Oseltamivir	£11,437
	Usual care	
9.	Oseltamivir	£16,127
	Amantadine	
10.	Oseltamivir	Oseltamivir and zanamivir are equivalent
	Zanamivir	

Conclusion

It is cost effective to treat all three population groups with oseltamivir for post exposure prophylaxis. In the seasonal setting the at risk populations are cost effective compared to usual care, amantadine and zanamivir, falling well below a CE threshold of £20,000.

The probabilistic sensitivity analyses for the PEP analyses demonstrated that there is a high probability of oseltamivir being cost effective when compared to usual care, amantadine or zanamivir in each of the populations. In the seasonal setting PSA also showed that there is a high probability of oseltamivir being cost effective in the at risk group.

The otherwise healthy analyses is also representative for otherwise healthy adults who work in care homes or with at risk individuals, these individuals are at in increased risk of developing and transmitting ILI in the household and at work. The at risk analyses are also representative for individuals in care homes as the preventative effectiveness rates used in the analyses are from a vaccinated elderly population in care facilities.