EXECUTIVE SUMMARY

Background

Oseltamivir is licensed for the treatment of influenza and for the post exposure and seasonal prophylaxis of influenza in adults and children one year of age or older. NICE have previously appraised oseltamivir for the treatment (TA 58) and prophylaxis (TA 67) of influenza and both of these appraisals are currently being reviewed. The Roche submission for the prophylaxis review focused upon the protection of people in a household setting against contracting influenza when there is an index case in a household.

Roche will therefore concentrate this treatment review will upon the index case in a household who will not be covered by a possible prophylaxis recommendation. In particular, robust evidence will be presented demonstrating that the treatment of healthy adults with oseltamivir is both clinically and cost effective compared to both usual care and zanamivir.

Influenza

The financial impact of influenza on society is due mainly to the loss of working time and reduced productivity. In the UK it was estimated that seasonal influenza leads to 779,000 to 1,164,000 GP consultations, 19,000 to 31,200 hospital admissions and 18,500 to 24,800 deaths annually. In primary care, the bulk of the burden falls on those under the age of 45 but the elderly are more likely to be hospitalised or die.

Clinical diagnosis of influenza can be challenging. There are also a number of laboratory and bedside diagnostic tests available. In the United Kingdom, local surveillance is coordinated by the Health Protection Agency. Historically, baseline threshold levels have been utilised to indicate increased seasonal activity. Initially the rationale for baseline levels was related to the communication of influenza activity to the media and general public. Arguably however, use of the baseline levels in a clinical context may be denying vulnerable patients treatment.

There are two main options for the management of influenza, these being prevention using vaccination or prophylaxis with antiviral agents and treatment with antiviral agents. Vaccination is generally recommended for high-risk groups, their care-givers and healthcare professionals. There are currently two classes of antiviral agents used for the treatment and prevention of influenza, these being the M2 channel inhibitors (amantadine and rimantadine) and the neuraminidase inhibitors (Tamiflu® (oseltamivir) and Relenza® (zanamivir, GSK).

Demonstrating the Clinical Effectiveness of Oseltamivir

Oseltamivir is the only licensed oral neuraminidase inhibitor for the treatment and prevention of influenza. It is well tolerated with the most frequently reported adverse events being nausea and vomiting which are usually mild and transient.

In clinical trials in healthy adults and adolescents, treatment with oseltamivir significantly reduces viral load and inflammatory markers associated with influenza. The duration and severity of influenza illness are considerably reduced along with a significant improvement in the time to return to normal health and everyday activity.

Treatment with oseltamivir is also associated with a reduction in the incidence of influenza-related complications and a clinically and statistically significant odds reduction of 15 day mortality. In children and adults, it has been shown that the benefits of oseltamivir treatment are significantly increased, the earlier it is taken post symptom onset.

In the paediatric setting, treatment with oseltamivir was also shown to significantly reduce the severity and duration of influenza illness and shorten the time to return to normal health, levels of sleep and everyday activity. Importantly in children, oseltamivir uniquely reduces the incidence of influenza-related complications in children for otitis media (OM) and for asthmatic exacerbations. In “at-risk” patients (the elderly and those with comorbid disease) oseltamivir treatment is associated with a reduction in the duration and severity of symptoms and a reduction in the incidence of complications. In the management of institutional outbreaks, statistically significant benefits were seen (such as a reduction in the occurrence of serious complications and mortality,

Resistance inevitably arises to some degree to all anti-infectives and is a potential issue of future interest. Roche have sought to be extremely diligent in the study and surveillance of resistance to oseltamivir. In the current influenza season, a higher prevalence of oseltamivir resistance in influenza A (H1N1) viruses with a specific neuraminidase mutation (H274Y) has been detected. Roche is committed to continued close monitoring of the current situation.

Demonstrating the Cost Effectiveness of Oseltamivir

We have evaluated the cost effectiveness of oseltamtivir in the settings being appraised using a probabilistic economic model based on a decision tree approach. The model allows for the cost effectiveness of oseltamivir compared to zanamivir and usual care for the treatment of influenza 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 and 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 only evaluates oseltamivir compared to usual care, as zanamivir is not licensed for use in this age group. Consequently a total of 7 incremental cost effectiveness ratios (ICERs) are reported reflecting the 2 methods of treatment, 2 potential comparators and the 4 discrete age related sub groups of interest.

For the oseltamivir and zanamivir analyses, oseltamivir and zanamivir are assumed to be equally effective at treating influenza. Based on this assumption a cost minimisation analysis is run for these comparisons whereas a cost utility analysis is performed for the usual care comparisons.

Results

Economic case		Incremental cost effectiveness ratio (ICER)
Otherwise healthy adults		
1.	Oseltamivir	£5,452
	Usual care	
2.	Oseltamivir	Oseltamivir is cost saving, saving £0.19 per patient
	Zanamivir	
Otherwise healthy children 1-12 years		
3.	Oseltamivir	£5,992
	Usual care	
4.	Oseltamivir	Oseltamivir is cost saving, saving £5.65 per patient
	Zanamivir	
Otherwise healthy children 1-5 years		
5.	Oseltamivir	£4,687
	Usual care	
At risk adults		
6.	Oseltamivir	£652
	Usual care	
7.	Oseltamivir	Oseltamivir is cost saving, saving £0.19 per patient

In the usual care comparisons oseltamivir is cost effective across each of the four patient groups with ICERs well below a cost effectiveness threshold of £20,000. Oseltamivir and zanamivir are equally effective at treating influenza; therefore the comparison of the drugs is based on costs. Zanamivir is consistently more expensive than oseltamivir across the patient groups resulting in oseltamivir being cost saving.

One way sensitivity analysis, scenario analysis and probabilistic sensitivity analyses demonstrated that the base case estimates were robust and that there is a high probability of oseltamivir being cost effective when compared to usual care across each of the sub-groups.

Estimating the cost effectiveness of oseltamivir from the societal perspective results in oseltamivir being dominant compared to usual care, more effective than usual care and less expensive, and cost saving compared to zanamivir.

Budget impact

On average around 779,000 general practice consultations are attributable to influenza each year. The annual drug cost of providing oseltamivir to both at risk and otherwise health individuals is estimated to be approximately £3.1m. The annual net cost is estimated to be slightly less than this (£3m) due to savings from the avoidance of ILI related complications more than offsetting the GP consultation cost related to prescribing oseltamivir.