28th March 2008

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BY E-MAIL

Dear Eloise,

Technology assessment report: oseltamivir, amantadine and zanamivir for the prophylaxis of influenza

Thank you for the opportunity to review and comment on the technology assessment report.

Please find below our comments on the analysis performed by the assessment group. We have raised a number of points for consideration by the appraisal committee which we feel requires further discussion at the appraisal committee meeting on April 23rd.

Best wishes.

Yours sincerely,

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Points for consideration

There are a number of differences between the assessment group's economic models and those submitted by Roche which we believe currently compromise the accuracy of the cost effectiveness estimates reported within the HTA assessment report.

The specific model assumptions and parameters which we will discuss in greater detail below are: (i) the preventative efficacy of vaccination, (ii) the assumed number of GP visits for prophylaxis, (iii) the assumed equivalent efficacy rates for oseltamivir and zanamivir, (iv) the probability of hospitalisation for influenza, (v) the assumption of resistance, (vi) the estimated drug costs and briefly comment on (vii) the probability that ILI is true influenza, (viii) the probability that patients will present within 48 hours, (ix) the practical implementation of the assessment report findings and (x) the estimated budget impact.

(i) Preventative efficacy of vaccination

The assessment group model assumes that vaccines are 58% effective for elderly, 65% for otherwise healthy adults and 64% effective for children at preventing influenza. Roche believes that these assumptions are valid only when seasonal mis-match has not occurred and may be too high for certain sub-groups such as the elderly and paediatrics.

There are a number of publications which illustrate some of the problems with regard to reduced effectiveness associated with vaccination against Influenza;

- UK HPA website (Cooke et al 2005) cites effectiveness of between 38 and 52% in adults and children in the UK in season 2003 to 2004 due to virus/ vaccine mis-match
- Jefferson 2005 : < 22% in prevention of respiratory admissions amongst community-dwelling elderly
- Goronzy 2001 : in elderly - only 17% of vaccine recipients in this study generated an increase in antibody titre to 3 vaccine components and 46% failed to respond to any of the 3 haemagglutinins used in vaccination. Successfulness of vaccination declining with age.
- Carrat 2007 – in this publication, vaccine mis-match is cited to have impact on vaccine effectiveness caused by antigenic drift – mis-match had significant epidemiological and economical consequences in the 1997-1998 season where mis-match occurred.
- Boschini 2006 – an outbreak of flu was studied in a residential drug-rehabilitation community in 2004. The attack rate in the sample size of 1310 studied was found to be higher than that typically found in HIV-infected persons. The author stated vaccination was ineffective because of the mis-match between wild and vaccine strains.

- De Jong 2000 – A mis-match between the influenza vaccine and the major epidemic of influenza A (H3N2) occurred in 1997-1998 season was cited as the cause for inadequately vaccinated elderly.
- Beyer 1993 – In 1992, 2/3rds of the population of a nursing home in Amsterdam was vaccinated. However in March 1993 an outbreak of Influenza occurred with a morbidity rate of 49% and a mortality rate of 10%. The Flu virus was A/H3N2. Failing vaccine effectiveness was attributed to mis-match with the circulating virus.

  It is well documented that vaccination has a decline in efficacy in an aging population. This in combination with frequently mismatched vaccine with circulating influenza strains indicated that the preventative efficacy of vaccination in the elderly population assumed in the assessment group model may need to adjusted downwards,

(ii) Assumed number of GP visits for prophylaxis

The Assessment Group's model assumes in the base case that each prescription of an anti-viral requires one GP consultation. Therefore, each individual requiring prophylaxis with anti-virals needs to consult the GP themselves.

The Roche submitted model was based on an average household of 4 individuals. Once an index case becomes ill with ILI they will consult the GP for treatment. The GP can then prescribe prophylaxis for each remaining member of the household once the GP is familiar with each member and is aware of their health background. The Roche model

therefore assumes one GP consultation per household, which is assumed to be on average 4 individuals.
The impact of this assumption on the post exposure prophylaxis cost effectiveness estimates is considerable and has been examined in the sensitivity analysis outlined in the Assessment Report. The table below summarises the base case estimates, assuming a GP consultation for every individual and the impact on the ICER when one GP consultation per household (4 individuals) is assumed.

Table 1: Estimated incremental PEP cost effectiveness ratios assuming one GP consultation per household (assessment report)

	Healthy children		**At risk children**		**Healthy adults**		**At risk adults**		**Healthy elderly**		**At risk elderly**	
	Unvacc	**Vacc**	**Unvacc**	**Vacc**	**Unvacc**	**Vacc**	**Unvacc**	**Vacc**	**Unvacc**	**Vacc**	**Unvacc**	**Vacc**
Post exposure prophylaxis												
Base case	**23,225 (Z)**	**71,648 (Z)**	**8,233 (Z)**	**27,684 (Z)**	**34,181**	**103,706**	**13,459**	**43,970**	**10,716**	**28,473**	**7,866**	**21,608**
Multiple prescriptions	19,634 (Z) 11,322 (O)	61,717 (Z) £38,627 (O)	6,797 (Z) 4,075 (O)	23,706 (Z) 14,428 (O)	17,161	55,124	6,017	22,704	4,897	14,651	3,327	10,894

As the table above highlights, changing this assumption to one GP consultation per household results in the ICER for oseltamivir reducing significantly. Notably oseltamivir becomes cost effective compared to zanamivir within the at risk and healthy elderly patient groups.
The ICER for oseltamivir was previously over a £30,000 threshold for at risk adults who were vaccinated, changing this assumption decreases the ICER to £22,704.
For healthy adults who are unvaccinated the base case was £34,181, changing the number of GP consultations per household reduces this ICER to £17,161.
The ICERs for healthy and at risk children using the base case assumption showed zanamivir to dominate the other prophylaxis options. Refining the GP consultation assumption shows oseltamivir to be cost effective compared to zanamivir across both healthy and at risk children groups, with ICERs ranging from £4,075 for at risk unvaccinated children to £38,627 for healthy vaccinated children.
Roche would request the appraisal committee evaluate what value the assumption of number of GP consultations per household should be for the ICER to fall below £30,000.

The evidence base for the one GP consultation per household assumption was taken from a Roche UK advisory board with influenza experts including Dr. Douglas Fleming, Dr. Murdo Macleod, Prof John Oxford and Dr. John Watkins. The attendees were of the opinion that for the purposes of post exposure prophylaxis GPs would provide prescriptions for a household at the one GP consultation.

As the model is evidently very sensitive to changes in this assumption it is Roche's belief that the assumption of one GP consultation per individual should be reconsidered as a base case assumption in the model. Roche recommends that this assumption requires greater discussion at the appraisal committee meeting where some expert opinion can be sought on the robustness of either of the above assumptions.

The assessment group model also assumes that for vaccinated patients a prophylaxis prescription can be given during the same consultation as the influenza vaccine. Therefore one GP visit is assumed for vaccination and prophylaxis. Based on the above assumption it is assumed that GPs will prescribe prophylaxis regardless of whether the patient needs prophylaxis or not.

It is Roche's belief that the current assumption in relation to the frequency of GP visits for the vaccinated populations within the HTA model is not reflective of clinical practice. Patients would receive influenza vaccination at the start of the generally accepted influenza season. At this time point influenza may not be circulating in the community and hence the prescription of an anti-viral for PEP would not be an appropriate assumption.

(iii) Equivalent efficacy rates for oseltamivir and zanamivir

The assumption of equivalent efficacy for oseltamivir and zanamivir as examined in the sensitivity analysis in the Assessment Report predominantly resulted in reducing the seasonal and post exposure prophylaxis ICERs.

Table 2: Estimated PEP ICERs assuming equivalent efficacy for oseltamivir and zanamivir (assessment report)

	Healthy children		**At risk children**	
	Unvacc	**Vacc**	**Unvacc**	**Vacc**
Post exposure prophylaxis				
Base case	**23,225 (Z)**	**71,648 (Z)**	**8,233 (Z)**	**27,684 (Z)**
Best case efficacy for NIs	630,864 (Z) £18,875	1.7m (Z) £59,607	252,401 (Z) 6,491	705,940 (Z) 22,858

	(O)	(O)	(O)	(O)

As the table above illustrates changing this assumption impacts the healthy and at risk children ICERs to a considerable extent. The base case analysis in these patient groups found zanamivir to be more cost effective than oseltamivir. Assuming that oseltamivir and zanamivir are equivalently effective results in oseltamivir being more cost effective than zanamivir across both patient groups vaccinated and unvaccinated.

Table 3: Comparison of preventative efficacy values identified in the Roche and ScHARR economic models (assessment report)

Seasonal	**Assessment Group assumptions**	**Roche assumptions**
Amantadine (across all patients groups)	0.60	0.54-0.67
Oseltamivir		
OHA	0.76	0.76
Children	0.76	0.72
Elderly	0.92	0.92
Zanamivir		
OHA	0.68	0.81
At risk adults	0.68	0.72
Children	0.83	0.97
Elderly	0.80	0.97
PEP	**Assessment Group assumptions**	**Roche assumptions**
Amantadine (across all patients groups)	0.90	0.48-0.67
Oseltamivir		
OHA	0.81	0.81
Children	0.64	0.64
Elderly	0.81	0.92
Zanamivir		
OHA	0.79	0.75
Children	0.79	0.64
Elderly	0.79	0.97

The modelling performed by the assessment group in the PEP setting for healthy children and at risk children, has shown amantadine and oseltamivir to be dominated by zanamivir. Upon reviewing table 32, page 150, it would appear that the assessment group have accepted the relative risk of contracting influenza following PEP for oseltamivir in healthy children and at risk children to be 0.36 and 0.36 respectively. The RRs of 0.36 have been derived from sub-group analyses of the paediatric group from the household study by Hayden et al (2004) as stated in the report section 5.2.2.2.2, page 84. However, the RR used for the paediatric groups when modelling zanamivir were taken from the mixed group

studies of adults and children from Hayden (2000), Kaiser (2000) and Monto (2002) with no specific sub-group analyses performed for the paediatric groups.

As increased viral shedding is well-documented in the paediatric setting with expected lower efficacy of anti-virals compared to the adult setting, it would be inappropriate and inconsistent to extrapolate data from mixed paediatric and adult data to the paediatric groups for zanamivir and use the paediatric specific data for oseltamivir. Therefore to apply mixed adult/paediatric efficacy data to represent paediatric efficacy biases this analysis in favour of zanamivir.

Roche would suggest that sub-group analyses are performed in the defined paediatric setting using the databases that informed the Hayden (2000), Kaiser (2000) and Monto (2002) studies to enable a less biased comparison be made between the anti-virals within the paediatric setting. Alternatively, Roche would suggest using the adult oseltamivir RRs for paediatrics to ensure a like for like comparison of the efficacy of the anti-virals.

The Roche model assumed that oseltamivir and zanamivir were equally effective in influenza prophylaxis. This assumption was based in part upon the available evidence. As the table above highlights there is very little difference in the preventative efficacies across oseltamivir and zanamivir, and in part due to expert clinical opinion at a UK advisory board. It was generally felt by the attendees that oseltamivir and zanamivir are equally effective in influenza prophylaxis.

This assumption is key in determining the most realistic cost effectiveness estimates that will help inform the appraisal committee's decision. As such the assumption of equivalent efficacy for oseltamivir and zanamivir requires further discussion and validation with input from influenza experts.

(iv) Probability of hospitalisation for ILI

The probability of hospitalisation for influenza has been excluded from the ScHARR economic model. This assumption is not representative of clinical practice as patients can be hospitalised for influenza and not just influenza complications like bronchitis or pneumonia. The probability of hospitalisation due to influenza for patients treated with usual care is not well documented however there is data available to show that patients with influenza do require hospitalisation. This lack of robust data makes it difficult to realistically estimate influenza specific probabilities. As documented in the Roche submission the influenza related probability of hospitalization (1.9%) was taken from Cox et al (2000)**.** The study estimates excess pneumonia and influenza hospitalizations from National Hospital Discharge Survey Data from 26 influenza seasons (1970–1995).

This study is based on US health care data however it was assumed that these probabilities would not differ for UK patients.

The exclusion of the probability of hospitalisation for influenza from the base case estimates has a considerable impact on the cost effectiveness estimates as shown in the assessment report sensitivity analysis, summarised in the table below.

Table 4: Estimated incremental seasonal and PEP cost effectiveness ratios assuming 10% of influenza illness that is uncomplicated require hospitalisation (assessment report)

Assumptions	Healthy children		At risk children		Healthy adults		At risk adults		Healthy elderly		At risk elderly	
	Unvacc	Vacc	Unvacc	Vacc	Unvacc	Vacc	Unvacc	Vacc	Unvacc	Vacc	Unvacc	Vacc
Seasonal prophylaxis												
Base case	**44,007**	**129,357**	**16,630**	**51,069**	**147,505**	**427,184**	**63,552**	**186,651**	**49,742**	**121,728**	**38,098**	**93,763**
10% uncomplicated hospitalisation	35,111	103,495	8,341	41,402	110,466	379,639	47,704	166,024	35,219	103,957	27,159	80,480

	Healthy children		At risk children		Healthy adults		At risk adults		Healthy elderly		At risk elderly	
	Unvacc	Vacc	Unvacc	Vacc	Unvacc	Vacc	Unvacc	Vacc	Unvacc	Vacc	Unvacc	Vacc
Post exposure prophylaxis												
Base case	**23,225 (Z)**	**71,648 (Z)**	**8,233 (Z)**	**27,684 (Z)**	**34,181**	**103,706**	**13,459**	**43,970**	**10,716**	**28,473**	**7,866**	**21,608**
10% uncomplicated hospitalisation	£3,485 (Z)	£51,937 (Z)	696 (Z)	20,165 (Z)	2,920	72,366	430	30,956	O dominates	16,207	O dominates	12,411

In the seasonal prophylaxis setting a change in this assumption results in the ICER for oseltamivir in at risk unvaccinated elderly decreasing from £38,098 to £27,159.
In the post exposure prophylaxis setting, assuming 10% of uncomplicated influenza requires hospitalisation decreases all the ICERs. In the healthy and at risk unvaccinated elderly oseltamivir is more effective and less expensive than any other prophylaxis option.

Although the assumption tested in the sensitivity analysis that 10% of patients with uncomplicated influenza require hospitalisation may be too high for some patient groups, the base case cost per QALY estimates currently

assumes no hospitalisation for influenza. Roche would argue this assumption is not representative of the illness and so should not be used to inform the base case estimates.
Also, as illustrated in the sensitivity analysis the models are very sensitive to changes in this assumption, with cost per QALYs falling from £34,181 to £2,920.

(v) Resistance

The assessment groups base case models assumed resistance to amantadine at a rate of 37%. In the sensitivity analysis the impact of resistance to oseltamivir is examined with a range of 10% - 50% resistance. No sensitivity analysis of the impact of resistance upon zanamivir was undertaken by the HTA group which Roche believe is not a fair evaluation reflective of the available evidence base.

Resistance inevitably arises to some degree to all anti-viral drugs. As a result, Roche have sought to be extremely diligent in the study and surveillance of resistance to oseltamivir. All Roche sponsored clinical trials of oseltamivir treatment and prophylaxis in adults and children for seasonal influenza included a detailed study of the emergence of viral drug resistance. In addition Roche (in partnership with GSK) have funded and encouraged world-wide surveillance work supported by WHO and others to assess the potential for the emergence of neuraminidase inhibitor-resistant viruses as part of the circulating wild type virus population.

In clinical trials both pre-and post-registration comprehensive data on the potential for the emergence of resistant virus has been obtained for over 1,700 oseltamivir-treated patients. All last culture positive virus samples from treated patients were assessed for the emergence of resistance by a standard phenotypic assay and, for almost all studies, any culture positive samples taken on or beyond day 4 of treatment were also assessed by genotyping such that minor (to about 20%) resistant sub-populations could be detected. The cumulative data to date from treatment studies give an overall incidence of resistance of 0.32% (4/1245) for adults and adolescents (0.4% if sub-populations detected only by genotyping are included) and 4.1% (19/464) for children (5.4%, 25/464 including genotyping). (Aoki F et al; 2007)

In contrast to the data for oseltamivir, there are no reports of resistance to zanamivir in clinical trials or clinical usage arising in immunocompetent patients. However, on the evidence of published literature, viruses from very few patients have been studied in this regard. For adult treatment studies NAIB2005 and NAIB2008 virus from 15 and 12 zanamivir-treated patients respectively were examined. In a further study in adults virus from 17 zanamivir-treated patients was studied. A study of treatment and

prophylaxis within the family setting provides data on 18 treated patients (9 index cases and 9 contacts). In the report of a study of the treatment of children aged 5-12 years viral susceptibility data is given for 9 zanamivir-treated patients (NB this age group does not include those,1-4 years, in whom the large majority of resistance to oseltamivir was selected). Thus with data from only 62 adults and 9 children 5-12 years of age it is unlikely that resistance at the level found for oseltamivir in seasonal influenza trials would have been detected.

In 1999, the Neuraminidase Inhibitor Susceptibility Network (NISN) was established to monitor for the potential emergence of neuraminidase inhibitor resistant virus becoming part of the circulating virus population post-launch of oseltamivir and zanamivir. NISN is composed of influenza specialist academics and senior representatives of all four WHO world influenza surveillance laboratories. It works in conjunction with and with the co-operation of the WHO.

Worldwide reports of neuraminidase inhibitor resistance have remained low. In response to the extensive use of oseltamivir in Japan since 2003, NISN have specifically monitored influenza virus isolates collected by 74 local public health laboratories in Japan and resistance levels have remained below 5%.

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. Current WHO worldwide surveillance data estimates resistance rates of approximately 13%. Foci of increased prevalence have occurred in specific geographical regions in particular in Norway (66%). This increased detection of resistance has been unrelated to the use of oseltamivir indicated for example, by the comparatively low prevalence of resistant isolates in Japan. Roche is committed to continued close monitoring of the current situation. (World Health Organisation H1N1 influenza resistance update http://www.who.int/csr/disease/influenza/h1n1_table/en/index.html)

At this point in time there is little published data on resistance to select N1 viruses that are resistant to zanamivir. A recent study in Australia published by Hurt et al (2007) identified several H1N1 strains that demonstrate significant resistance to zanamivir (up to 250 fold) through Q136K and K150T mutations. These 4 zanamivir resistant virus strains showed little or no change in susceptibility to oseltamivir.

To date oseltamivir has been used effectively and with a good tolerability profile in over 48 million people worldwide, including 21 million children. Zanamivir has been used in 3.99 million people worldwide (based on sales data) and this estimate is inclusive of government stockpiles for pandemic

influenza preparedness where drug has not yet been taken by patients and remains in storage. (Glaxosmithkline FDA pediatric advisory committee meeting November 27th 07). It may be important to consider the extent of drug exposure and usage in relation to levels of resistance.

A combination of low levels of zanamivir usage and lack of investigation into zanamivir resistance relative to the volume of data available on oseltamivir makes a comparison across these two anti-virals extremely difficult and biased.

Roche strongly believes that resistance to zanamivir is a possibility and therefore the resistance sensitivity analysis should also be applied to zanamivir.

(vi) Estimated drug costs

The Assessment Group estimated the cost of amantadine, oseltamivir and zanamivir across the patients groups for seasonal and post exposure prophylaxis. Drug wastage is captured in the cost estimates. Roche believe that the seasonal drug costs for oseltamivir in paediatrics is overestimated. The table below provides a summary of what Roche considers the most appropriate drug cost estimates to be for these patient groups.

Table 5: Estimated oseltamivir drug costs for paediatrics

Oseltamivir	Drug cost	Description
Children 1-12 years	£49.08	Average weight 25kg Recommended dose: 60mg once daily for 6 weeks 60mg*42 = 2,520mg One bottle suspension = 900mg Therefore 3 bottles required Cost per bottle £16.36 Total cost = £49.08
Children 1-5 years	£49.08	Average weight 16kg Recommended dose: 45mg once daily for 6 weeks 45mg*42 = 1,890mg One bottle suspension = 900mg Therefore 3 bottles required Cost per bottle £16.36 Total cost = £49.08

The Assessment Report estimates drug costs for oseltamivir in children to cost £73.65. It is not clear how this cost has been derived.

(vii) Probability that ILI is true influenza

It is assumed in the assessment group's model that 50% of ILI is true influenza. However in areas where influenza isolates are identified, through national surveillance, true influenza can be assumed. Therefore, this proportion could be much higher in such instances.

(viii) Probability that patients present within 48 hours

The assessment group assumes that 52% of paediatrics, 16% of otherwise healthy adults and 11% of elderly present within 48 hours. This is in contrast to the Roche model which is based on the assumption that those patients who present after 48 hours will be filtered out via consultation with their GP. Therefore 100% compliance to the licensed indication is assumed and the evaluation relates to the cost effectiveness of prophylaxing patients who present within the 48 hour period. Patients who do not present within 48 hours, and are thus outside of the licensed indication, would not receive oseltamivir and do not form part of the economic evaluation. Whilst it is well acknowledged that treatment within 48 hours is important in the treatment setting the impact of this treatment rule upon efficacy in the PEP setting is less certain.

(ix) The practical implementation of the assessment report findings

The assessment report found zanamivir to be the most cost effective prophylaxis option in healthy and at risk children, both vaccinated and unvaccinated, also in some of the sensitivity analysis zanamivir was found to be the most cost effective prophylaxis option in some at risk populations. It is worth noting that as per the zanamivir SPC it has not been possible to demonstrate the efficacy and safety of zanamivir in patients with severe asthma or with other chronic respiratory disease, patients with unstable chronic illnesses or immunocompromised patients who have been treated. Due to limited and inconclusive data, the efficacy of zanamivir in the prevention of influenza in the nursing home setting has not been demonstrated. The efficacy of zanamivir for the treatment of elderly patients ≥65 years has also not been established

Should zanamivir be considered appropriate for patients with asthma or chronic obstructive pulmonary disease, the patient should be informed of the potential risk of bronchospasm with zanamivir and should have a fast acting bronchodilator available. Patients on maintenance inhaled bronchodilating therapy should be advised to use their bronchodilators before taking zanamivir

(x) Budget impact estimates

It is indicated in the report that the population has been multiplied by the attack rate to calculate the number of individuals likely to receive PEP. However it is not clear from table 79 that this is the case. For instance using this method would give 2.2 million (8.8% * 25,110,750) healthy adults expected to receive PEP not the stated 5 million.

For the proposed method of calculating the incidence of ILI to be accurate the attack rate would need to represent the probability of an individual contracting ILI in a given year. However the attack rate of 41% assumed for residential care homes represents the probability of an individual contracting ILI in an affected care home. Thus one would need to multiply this figure by the probability of a care home being affected in an average year. It is not evident from the report that this has been done and brings into question the appropriateness of the attack rates applied to the other groups.

From a face validity perspective the incidence figures in the report appear to be an overestimate. In a recent 2007 publication by Pitman et al (Commissioned by the Department of Health) it was estimated that 779,000 general practice consultations are attributable to influenza infections in the England and Wales. From table 79 it appears that the assessment group has estimated 10.7 million individuals requiring PEP. This would seem to be unlikely given the current number of GP consultations as it would mean around 14 PEP prescriptions per current ILI GP consultations.

Given that 779,000 people currently consult the GP for ILI and there are on average 4 people per household one might expect around 2.3 million individuals [779,000 * (4 – 1)] requesting PEP, effectively 22% of the number estimated by the assessment group.

We request that a full description of how the additional budget impact has been calculated from the incidence rates in table 79 as it is currently not clear from the report.

Summary

As highlighted above the model is very sensitive to changes in any one of the above assumptions. A change in a combination of these assumptions would considerably impact the final incremental cost effectiveness ratios. It is Roche's belief that these assumptions need to be discussed in detail at the appraisal committee meeting where input from clinical experts can help identify the most realistic assumptions and therefore inform which final cost per QALYs should be used as a basis for decision making.

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