



Tuesday 29th July 2008
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BY E-MAIL

Dear Amy,

**MULTIPLE TECHNOLOGY APPRAISAL –
Influenza (treatment) – amantadine, oseltamivir and zanamivir:
Response to Assessment Report**

Thank you for sending us the assessment report for the above technology appraisal. Our response is provided below.

Indirect comparison of clinical effectiveness in “at-risk” population

Roche agrees with the assessment report conclusions that there is uncertainty relating to the comparative effectiveness of zanamivir and oseltamivir. Considering the level of heterogeneity in the zanamivir and oseltamivir “at risk” studies, Roche considers the assessment report conclusion that within the ‘at risk’ population: ‘zanamivir appeared the optimal NI treatment based on cost-effectiveness considerations’ not to be based on a robust evidence base of the comparative clinical effectiveness.

Data relevant to time to alleviation of symptoms and return to normal activities summarized in Figure 5.2, 5.3, 5.9 and 5.10 do not enable like-for-like comparisons of oseltamivir and zanamivir. For example the symptoms assessed by the two trial sponsors (F.Hoffmann – La Roche and GSK respectively) differ (Turner et al 2003, table 10, p43). A summary of the typical variations in study characteristics contributing to the heterogeneity are provided in appendix 1 below.

The “high risk” groups studied with respect to time to alleviation of symptoms differed significantly in composition: the zanamivir group (N=253) largely consisted of asthma and COPD patients (63% of total) in study NAI30008 (N=160), while the oseltamivir group (N=557) was dominated (64% of total) by subjects who were “otherwise healthy 65 years and older” (N=358).

When 'time to return to normal activities' are evaluated, consideration should be given to the fact that the oseltamivir group was again largely composed of otherwise healthy individuals >64 years of age, while the zanamivir group was dominated by known COPD and asthma patients; any comparison between the two groups is therefore confounded by these differences, as the effects of these differences are unclear, it may be argued that the difference might benefit the zanamivir group, which might be expected to have gained the most benefit from any efficacious intervention. Despite this, oseltamivir appears to show superiority to zanamivir: when oseltamivir was compared to placebo statistically significant benefit was seen not only in the influenza positive group, but also in the intention to treat (ITT) population; no statistically significant effect could be found for zanamivir in either population.

Roche would strongly encourage that the committee discuss the heterogeneity of the trials included in the comparative clinical effectiveness analysis. Furthermore to what extent this heterogeneity may influence the reliability of the Bayesian multi-parameter evidence synthesis adopted by the assessment group.

In addition to the cost effectiveness evidence, Roche recommend 2 other issues are considered by the committee in their deliberations.

Practical considerations for recommendations for at risk groups

The current assessment report evaluation of the evidence base suggests that zanamivir is the preferred treatment within the "at risk" population based upon the economic evaluation. Roche would like to highlight key issues for consideration in the preparation of any guidance for the NHS.

Patients at a high risk of influenza-associated complications include the elderly, patients with chronic respiratory disease or cardiac disease and the immunocompromised. In addition children under 1 year of age are also high risk and arguably young children per se.

According to the zanamivir summary of product characteristics, the efficacy of zanamivir has not been established in the elderly (≥ 65 years).

Experts and the WHO have serious concerns over the use of zanamivir in some patients with respiratory problems, as inhalation of the drug has been associated with bronchospasm (WHO 2007). The current NICE recommendation is that zanamivir should be used with caution in people with asthma or chronic pulmonary disease, as well as in people with unstable chronic illness or compromised immune systems. It is recommended that these patients be made aware of the risks and have a fast-acting bronchodilator available. In patients with severe asthma, zanamivir should only be administered under close medical supervision [NICE 2003; Relenza SPC].

In addition there have been very rare reports of patients being treated with zanamivir who have experienced bronchospasm and/or decline in respiratory function which may be acute and/or serious in which the patients did not have any previous history of respiratory disease.

Oseltamivir can be used with no special cautions in patients with respiratory disease.

Furthermore, oseltamivir has been used safely in asthmatic children with seasonal influenza. A benefit on influenza illness duration approached statistical significance when treatment was commenced <24 hours after symptom onset (25% reduction; $p=0.078$) [Johnston et al. 2005]. Moreover, oseltamivir-treated patients experienced significantly fewer asthma exacerbations — the major driver of asthma morbidity and costs.

Mode of administration

In addition to the regulatory considerations outlined above, the method of administration for zanamivir and oseltamivir should be fully considered within the preparation of any guidance for the at-risk population.

Oseltamivir is taken by mouth and is available commercially in a variety of formulations designed to facilitate its weight-based dosing in children (30, 45 and 75 mg capsules and a powder for suspension).

Zanamivir inhalation powder is packed in a circular aluminium foil disk (a Rotadisk®) with four regularly distributed blisters each containing zanamivir 5 mg. The inspiration-driven Diskhaler® device is used for administration of doses (the contents of two blisters constitute a dose). The inhaler must be primed and loaded prior to inhalation.

Most patients and carers will require tuition in the use of the Diskhaler®, for example by a nurse or pharmacist. Despite tuition, many patients may not be able to use the Diskhaler® properly. Dose-count compliance rates of 97% have been reported in clinical trials of inhaled zanamivir [Monto et al. 1999], while a patient-reported compliance rate of 75% was reported in a clinical practice survey [Bricaire et al. 2002] However, many patients may have difficulty in loading the Diskhaler® device in clinical practice. Even after tuition, 50% of hospitalised elderly patients with unimpaired cognitive function ($n=38$) in an independent UK study were unable to load and prime the zanamivir Diskhaler®; 65% were unable to do so 24 hours later [Diggory et al. 2001]. Another study reported that 70% (100/140) of elderly residents in long-term care were willing to try the zanamivir Diskhaler® and had no problem using it. However, the ability to use the device was dependent on functional and mental status, with 58% of patients fully dependent on care for daily activities having difficulties [Lee et al. 2000]. In the community setting, elderly patients with influenza (and any patients with cognitive impairment) are even more unlikely to be able to use the device correctly.

The usage of the Diskhaler® might also be problematic in children. In addition to the tuition requirements, and difficulty of administration for some young children, there is also the generation of sufficient peak inspiration flow rate to activate the device that needs to be taken into consideration [SPI 2008]. In principle, suboptimal exposure to treatment could risk the development of drug resistance, as well as treatment failure.

Consequently a recommendation for zanamivir only in the at-risk groups based a highly

uncertain economic evaluation would not adequately account for the practical issues of the method of administration and regulatory restrictions associated with zanamivir.

Yours sincerely,



References

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Diggory P, Fernandez C, Humphrey A, et al. (2001). Comparison of elderly people's technique in using two dry powder inhalers to deliver zanamivir: randomised controlled trial. *BMJ* 2001;322;577-580.

Johnston SL, Ferrero F, Garcia ML, et al. (2005). Oral oseltamivir improves pulmonary function and reduces exacerbation frequency for influenza-infected children with asthma. *Pediatr Infect Dis J*; 24: 225-32

Lee C, Loeb M, Phillips A, et al. Zanamivir use during transmission of amantadine-resistant influenza A in a nursing home. *Infect Control Hosp Epidemiol* 2000;21:700–4

Monto AS, Webster A, Keene O. Randomized, placebo-controlled studies of inhaled zanamivir in the treatment of influenza A and B: pooled efficacy analysis. *J Antimicrob Chemother.* 1999;44 Suppl B:23–9

National Institute of Clinical Excellence. (2003). Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza. Technology Appraisal Number 58.

Relenza Summary of Product Characteristics. (2008)

Scientific Pandemic Influenza Advisory Committee. (2008). Request for scientific advice on stockpiling neuraminidase inhibitors.

WHO Clinical management of human infection with avian influenza (H5N1) virus. (2007)

Appendix 1: Summary of published study characteristics included in assessment group meta-analysis

	Tamiflu (2 studies)		Zanamivir (6 studies)			
	Martin	Johnson	NAI130012 Trial no info	MIST	Boivin	Hedrick
No of patients enrolled	1138	335		455	35	471
Time from onset of symptoms to treatment	36hrs	48hrs		36hrs	48hrs	36hrs
Criteria for flu- fever	y	y		y	y	y
Criteria for flu- other symptoms	1 systemic/ 1 resp	1 resp		2 others	2 others	none
Adults	y	n		y	y	n
Children	n	6-12		n	n	6-12
Vaccinated patients	111 at-risk 315 elderly	65 ITT 25 ITTI		26 ITT 15 ITTI	?	11 ITT 3 ITTI
Study includes healthy and at-risk	n	n		y	y	y
At-risk groups included	elderly cardiac/respiratory	asthma		respiratory/>65 endocrine/cardiac	elderly/renal respiratory/cardiac	respiratory
No of at-risk patients - placebo ITT	elderly 376 at risk 203	164		39	2	14
No of at-risk patients- antiviral ITT	elderly 360 at risk 199	170		37	1	22
No of at-risk patients - placebo ITT with confirmed flu	elderly 254 at risk 133	95		38		
No of at-risk patients- antiviral ITT with confirmed flu	elderly 222 at risk 118	84		24		
Time to alleviation of symptoms - placebo ITT				8.0 days		all pts 5days
Time to alleviation of symptoms - antiviral ITT				5.5 days		all pts 4.5days
Time to alleviation of symptoms - placebo ITTI	at risk-fever/chills 57.9hrs fever/cough 117.3hrs elderly-fever/chills 50.5hrs fever/cough 132.3hrs	134.3hrs		8.25 days	all pts - 9.5 days	all pts 5.25days
Time to alleviation of symptoms - antiviral ITTI	at risk-fever/chills 40.8hrs fever/cough 96.0hrs elderly-fever/chills 36.0hrs fever/cough 115hrs	123.9hrs		5.0 days	all pts - 5.0 days	all pts 4.0days
Time to return to normal activity - placebo ITTI	n/a	114hrs				
Time to return to normal activity - antiviral ITTI		101.4hrs				