ORIGINAL RESEARCH ARTICLE

Pharmacoeconomics 2001; 19 (3): 293-301
1170-7690/01/0003-0293/$22.00/0

Cost-Effectiveness Analysis of Inhaled Zanamivir in the Treatment of Influenza A and B in High-Risk Patients

Adrian D. Griffin,[1] *Andrew S. Perry*[1] and *Douglas M. Fleming*[2]

1 GlaxoWellcome Research and Development, Greenford, UK
2 Northfield Health Centre, Birmingham, UK

Abstract

Objective: To evaluate the cost effectiveness of zanamivir 10mg twice daily for 5 days in the treatment of influenza in high-risk patients.

Design: Bootstrap cost-effectiveness analysis incorporating within-trial analysis of pooled patient-level cost and effect data.

Setting: UK unit costs and utilities applied to high-risk patients drawn from 6 multinational clinical trials.

Patients: A total of 154 zanamivir and 167 placebo high-risk patients were included in the analysis.

Main outcome measures: Cost per day of normal activities; cost per symptom-free day; cost per complication averted; cost per quality-adjusted life-year (QALY).

Results: The mean benefit was estimated to be 2.5 days [95% confidence interval (CI): 0.68 to 4.27] of normal activities gained; 2.0 (95% CI: 0.56 to 3.51) symptom-free days; and a 9% reduction in complications (95% CI: 0 to 18%). Excluding the effect of rare hospitalisation costs, the cost (1999 values) of gaining a day of normal activities was £9.50 (95% CI: £5 to £39); cost per symptom-free day was £11.56 (95% CI: £6 to £43); cost per complication averted was £262 (95% CI: £90 to £1574). Influenza was estimated to reduce utility by 0.883 per day, demonstrating the debilitating effect of the disease. Extrapolating a day of normal activities to a standard utility measure resulted in a cost per QALY of £3900 excluding inpatient costs (£7490 including inpatient costs). Cost-effectiveness acceptability curves demonstrated 90% certainty that zanamivir would be cost effective at £8000 per QALY.

Conclusions: Significant health benefits can be obtained with zanamivir treatment in high-risk patients. The cost per QALY for zanamivir in these patients compares well with that of other commonly used pharmacological interventions.

Influenza outbreaks occur almost every winter and result in high levels of morbidity and mortality. Results from a recent systematic review of the impact of influenza suggested that the average patient with influenza had a 3% chance of being hospitalised for 8 days, and resulted in over 5 working days lost.[1] Influenza is associated with additional morbidity or mortality in patients who are elderly and in individuals who have an underlying disease such as diabetes mellitus, asthma, chronic obstructive pulmonary disease (COPD) or cardiovascular disease. During the 1989/1990 influenza epidemic, over

25 000 excess deaths were estimated to have occurred in England and Wales, many of whom would have been aged over 65 years.[2]

Zanamivir, the first of a new class of antiviral agents, was developed as a highly potent and selective inhibitor of all known influenza A and B virus neuraminidases.[3] Delivered directly to the primary site of viral replication in the respiratory tract, zanamivir is an orally inhaled agent indicated for adults and adolescents presenting within 48 hours after onset of typical influenza symptoms when influenza is circulating in the community. Other neuraminidase inhibitors are in development but have yet to be licensed in Europe (oseltamivir is available in the US).

This economic evaluation analysed the cost effectiveness of zanamivir in the treatment of influenza in patients at 'high risk' of complications from the illness. International clinical and resource use data were coupled with UK unit costs and utility estimates. Previous zanamivir evaluations have relied on modelling outcomes for high-risk patients based upon the limited data available from individual clinical trials.[4] This method allows for a degree of freedom with sensitivity analysis but does not provide a measure of uncertainty around the cost-effectiveness ratio. The present evaluation was based on the results of a pooled analysis of 6 large randomised, placebo-controlled clinical studies[5] and uses a bootstrapping technique to generate 95% confidence intervals (CIs) around the resulting cost-effectiveness point estimates.

Methods

Patients

The cost-effectiveness analysis incorporated all studies in the main international clinical development programme up to the 1998/1999 season in which the licensed dose of zanamivir had been investigated and in which high-risk patients were recruited. This resulted in the inclusion of 5 influenza treatment studies and the treated cases from 1 mixed influenza treatment and prophylaxis study [NAIB2007,[6] NAIB3001,[7] NAIA3002,[8] NAIB3002,[9] NAI30009,[10] and NAI30010 (index cases only, not prophylaxis)].[11] Table I describes the studies and the recruitment of high-risk patients in each.

Each of the studies defined a group of patients as being 'high risk' if they had chronic respiratory disease (including asthma and COPD); significant cardiovascular disease (excluding patients with hypertension as the sole diagnosis); were immunocompromised; or were ≥65 years of age with or without underlying medical conditions. In addition, NAIB3001 and NAIB2007 included patients with diabetes mellitus. This definition is similar to that

Table I. Studies included in the analysis

Study	Description	Length of diary card (days)	All patients[a]		High-risk patients[a]	
			placebo (censored)	zanamivir (censored)	placebo (censored)	zanamivir (censored)
NAIB3001	Phase III, Southern hemisphere, 1997	14	228 (101)	227 (61)	39 (24)	37 (12)
NAIA3002	Phase III, North America, 1997-1998	28	365 (103)	412 (100)	60 (22)	49 (21)
NAIB3002	Phase III, Europe, 1997-1998	28	182 (71)	174 (45)	19 (9)	13 (2)
NAI30009	Phase III paediatric study, North America/Europe/Israel, 1999	28	247 (51)	224 (26)	14 (4)	22 (3)
NAI30010	Phase III family prophylaxis study with treatment for index cases, North America/Europe, 1998-1999 (only index cases included)	28	160 (14)	161 (17)	11 (1)	10 (2)
NAIB2007	Phase II, Southern hemisphere, 1995-1996	5	183 (150)	188 (132)	24 (20)	23 (12)
Total			**1365 (490)**	**1386 (381)**	**167 (80)**	**154 (52)**

a Number censored includes those with censored data for either 'time to return to normal activities' or 'time to alleviation of clinically significant symptoms'.

used to identify high-risk individuals appropriate for vaccination in the UK.

The evaluation was performed on the intent-to-treat (ITT) population, defined as all randomised patients regardless of whether study drug was received or whether the patient completed the planned duration of treatment.

End-Points

The end-points used in the evaluation were 'time to return to "normal" activities' as defined by the patient; 'time to alleviation of clinically significant symptoms'; and 'incidence of complications requiring use of antibacterials'.[5] Alleviation of symptoms was considered to have occurred when patients reported absence of fever (temperature <37.8°C and no feverishness), and recorded a symptom score of 'none' or 'mild' (or 'absent/minimal' in studies NAI30009 and NAI30010) for headache, cough, myalgia and sore throat. These conditions had to be maintained for a further 24 hours.

The most common complications requiring antibacterial use were acute bronchitis, acute sinusitis, pharyngitis, ear infection, pneumonia and worsening of influenza symptoms.

Data Collection

Patients rated their symptoms and ability to perform normal activities in a diary card. The duration of diary card collection in the 6 studies varied from 5 to 28 days. Since patients had to maintain their alleviated state for at least 24 hours (3 consecutive diary card entries), the latest recorded time to alleviation or return to normal activities was 1.5 days prior to end of follow-up. This meant that data from patients who were not alleviated during the course of the study were described as censored.

Resource use data were collected as part of the case record form (CRF). The investigator completed the CRF from patient records, irrespective of patient outcome. Resource use data were therefore not subject to censoring. Table I lists the length of follow-up in each study and the number of patients whose symptoms were not alleviated during follow-up.

Extrapolation of Censored Data

To enable CIs to be determined through bootstrap techniques (see 'Statistical Analysis' section), data were required for all patients, including those who were censored. It was therefore necessary to estimate the time to alleviation and time to return to normal activities for all censored data.

Mean survival times were estimated using standard Kaplan-Meier techniques, while adjusting for censoring. A randomly generated estimate of alleviation time was made for each censored value using survival analysis based on the distribution observed from the standard Kaplan-Meier plot of all patients in the integrated trial database. No extrapolation was made beyond the duration of the final censoring point in the longest trial (26.5 days). Kaplan-Meier methods are accepted as standard for both outcomes[12] and costing.[13]

Cost data were not extrapolated, as resource use data were collected by the investigator in the CRF for both censored and uncensored patients.

Utility Data

Utility values were not collected directly during the clinical trial programme. However, for the purposes of creating a cost per quality-adjusted life-year (QALY), utility estimates were collected from 2 sources.

(i) Typical general population patients (aged ≥18 years, n = 21) who experienced influenza infection (confirmed by virus culture) fewer than 3 months earlier during the 1999/2000 season were identified from a UK general practitioner (GP) database and asked to retrospectively complete one EQ-5D (EuroQoL instrument) health questionnaire[14] describing the entire period of their influenza illness and another EQ-5D for the most severe day within that period. The value describing the entire influenza period is used in the analysis.

(ii) As a check on the patient-generated values, a UK GP panel (n = 8) used the EQ-5D questionnaire to rate the health-state for a hypothetical influenza high-risk patient (these values were not used in the analysis).

In both cases, baseline (norm) health-state utilities were also obtained. Utility values were obtained by inputting each patient's scores for the 5 dimensions into a published algorithm.[15] This method of obtaining utilities has been established in other disease areas, such as multiple sclerosis.[16]

The QALY is calculated from the following equation:[17]

QALY = quality adjustment (Δutility) × time in state

For the QALY calculation, the time spent without normal activities was valued as the health-state with influenza. The rest of the year was valued at the norm. The difference in QALYs between the placebo and zanamivir groups was then calculated.

Healthcare Resource Use

For each patient in the studies identified, data were collected on all unscheduled healthcare contacts (GP, nurse, practice or home visit, etc.) as part of the CRF. Unscheduled contacts were defined as those not required as part of the study protocol. In addition, all prescription or over-the-counter (OTC) medications started on or after the day of randomisation were recorded.

Data on hospitalisations were not collected routinely as part of the CRF. Data concerning hospitalisations related to influenza were therefore gathered from the serious adverse event (SAE) forms reported by investigators (since hospitalisation for any reason is classified as a SAE for clinical trials).

Costs

Standard UK unit costs were applied to the unscheduled healthcare contacts and antibacterials used in the trials (table II). All costs are 1999 values. Discounting was not considered appropriate as all costs and benefits considered occur within 1 year.

Table II. Resource use and unit costs

Resource item	Resource use per patient		Unit cost (£; 1999 values)	Source (year)
	placebo	zanamivir		
Zanamivir (treatment course)	0	1	24.00	GlaxoWellcome UK
GP clinic visit	0.341	0.247	18.00	Netten et al.[18] (1999)
GP home visit	0.048	0.019	54.00	Netten et al.[18] (1999)
GP telephone contact	0.042	0.045	21.00	Netten et al.[18] (1999)
Nurse clinic visit	0.012	0.000	9.14	Netten et al.[18] (1999)
Nurse home visit	0.006	0.006	12.00	Netten et al.[18] (1999)
Nurse telephone contact	0.024	0.013	9.14	Netten et al.[18] (1999)
Outpatient visit	0.018	0.065	63.00	Netten et al.[18] (1999)
Other (as GP clinic visit)	0.012	0.000	18.00	Netten et al.[18] (1999)
Day in hospital	0.066 days	0.162 (0.058[a]) days	222.00	Netten et al.[18] (1999)
Penicillins (average course)	0.084	0.058	1.70[b]	Medical Data Index[19] and BNF[20]
Macrolides (average course)	0.072	0.078	4.25[b]	Medical Data Index[19] and BNF[20]
Cephalosporins (average course)	0.018	0.045	3.82[b]	Medical Data Index[19] and BNF[20]
Tetracyclines (average course)	0.036	0.000	1.92[b]	Medical Data Index[19] and BNF[20]
Other antibacterial (average course)	0.042	0.032	0.38[b]	Medical Data Index[19] and BNF[20]
Over-the-counter medication	0.419	0.506	1.50	Estimate from GlaxoWellcome market research
Total cost per patient	£27.21 (£12.59[c])	£72.15 (£36.11[c])		

a Excluding inpatient hospitalisation costs for 1 outlying patient who was hospitalised for pneumonia within 24 hours of recruitment.

b Antibacterial costs based on prescriptions written for influenza and pneumonia [International Classification of Diseases (ICD-10) codes J10 to J18].

c Excluding all inpatient hospitalisation costs.

BNF = British National Formulary; **GP** = general practitioner.

Table III. Mean incremental costs (1999 values) and effects for zanamivir in the treatment of influenza in high-risk patients. Values in parentheses are 95% confidence intervals

Effectiveness measure	Placebo	Zanamivir	Incremental effect	Incremental cost	ICER
Base case (including rare inpatient hospitalisations)					
Time to return to normal activities	11.96 days (10.64, 13.28)	9.48 days (8.26, 10.70)	2.48 days (0.68, 4.27)	£44.94 (–£8, £98)	£18.14 (£1, £85)
Time to alleviation of symptoms	9.09 days (7.96, 10.21)	7.05 days (6.09, 8.01)	2.03 days (0.56, 3.51)	£44.94 (–£8, £98)	£22.08 (£0, £97)
Incidence of complications	25% (18%, 31%)	16% (10%, 21%)	9% (0%, 18%)	£44.94 (–£8, £98)	£501 (–£94, £3234)
Sensitivity analysis excluding SAE hospitalisations					
Time to return to normal activities	11.96 days (10.64, 13.28)	9.48 days (8.26, 10.7)	2.48 days (0.68, 4.27)	£23.52 (£18, £29)	£9.50 (£5, £39)
Time to alleviation of symptoms	9.09 days (7.96, 10.21)	7.05 days (6.09, 8.01)	2.03 days (0.56, 3.51)	£23.52 (£18, £29)	£11.56 (£6, £43)
Incidence of complications	25% (18%, 31%)	16% (10%, 21%)	9% (0%, 18%)	£23.52 (£18, £29)	£262 (£90, £1574)
Sensitivity analysis excluding 1 hospitalised patient					
Time to return to normal activities	11.96 days (10.64, 13.28)	9.44 days (8.22, 10.67)	2.52 days (0.72, 4.32)	£21.67 (–£6, £49)	£8.61 (£3, £43)
Time to alleviation of symptoms	9.09 days (7.96, 10.21)	7.02 days (6.06, 7.99)	2.06 days (0.58, 3.55)	£21.67 (–£6, £49)	£10.50 (–£3, £49)
Incidence of complications	25% (18%, 31%)	16% (10%, 21%)	9% (0%, 18%)	£21.67 (–£6, £49)	£245 (£84, £1736)

ICER = incremental cost-effectiveness ratio; **SAE** = serious adverse event.

Statistical Analysis

All results are reported as means in incremental costs and effects with 95% CIs generated through a bootstrap method. The incremental cost-effectiveness ratio (ICER) is calculated from the difference in mean costs divided by the difference in mean effects. The nonparametric bootstrap method involved creating new 'trial populations' by resampling (with replacement) cost and effect pairs from the control and treatment samples and then calculating the cost and effect averages for each bootstrap sample. ICERs for each control and treatment sample could then be calculated. Bootstrap sampling was repeated 5000 times with the 2.5th and 97.5th percentiles interpreted as 95% CIs around the mean ICER from the original trial data.[21]

Cost-effectiveness acceptability curves were generated to allow decision-makers to see the probability of zanamivir being cost effective (y-axis) in relation to varying amounts they might be prepared to pay to secure the benefits (x-axis).[22-24] The curves are constructed by varying the maximum cost-effectiveness threshold and calculating the proportion of bootstrap resamples that would fall under each threshold.

The cost-effectiveness acceptability curve was also generated through the parametric 'net benefit' approach[25] in order to corroborate the nonparametric bootstrap method.

Results

A total of 2751 patients were recruited into the 6 studies and received zanamivir 10mg twice daily or placebo. Of these, 321 high-risk patients were included in the analysis (154 zanamivir, 167 placebo). Detailed results of the integrated analysis have been published elsewhere.[5] 159 patients (50%) were male. Mean age was 40.1 years with 76 (24%) aged 65 years or over. 227 (71%) were confirmed by laboratory methods as having influenza (105 zanamivir, 122 placebo). 74 (23%) of the 321 pa-

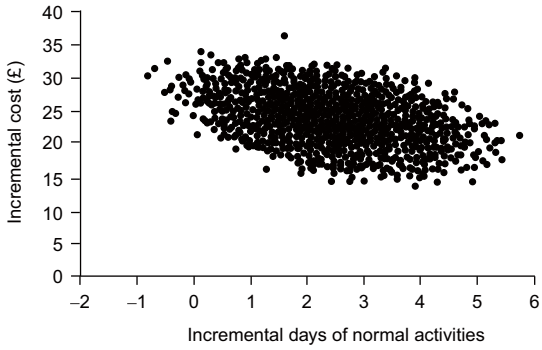

Fig. 1. Incremental cost-effectiveness plane. Plot of 5000 bootstrap incremental cost (1999 values) and effect (days of normal activities) resample means.

tients had been vaccinated against influenza (40 zanamivir, 34 placebo).

Extrapolation of Censored Data

The mean time to return to normal activities for all recruited patients (including high-risk) using the Kaplan-Meier product limit estimator was 8.8 days in the observed placebo group and 8.9 days after extrapolation. In the zanamivir group, the mean time to return to normal activities was 7.7 days both in the observed group and after extrapolation. The distribution containing extrapolated data closely overlaid the distribution based on observed data when plotted on a Kaplan-Meier graph.

Resource Use

Table II shows the level of healthcare contacts, hospitalisations, antibacterial use and OTC medications for the placebo and zanamivir groups.

The primary cost driver in the resource use calculations was the cost of hospitalisation. In the total trial population, there were 6 influenza-related hospitalisations in the zanamivir group and 4 in the placebo group. In the high-risk subpopulation, 4 hospitalisations occurred in the zanamivir group (2 pneumonia, 2 dehydration) and 2 occurred in the placebo group (1 pneumonia, 1 exacerbation of lower respiratory tract symptoms). Neither of these differences is statistically significant. A sensitivity analysis was therefore conducted which excluded the cost of hospitalisation. One patient in the zanamivir group was hospitalised for pneumonia within 24 hours of recruitment and withdrawn from the study. The underlying pathology behind this patient's pneumonia must therefore have been developing prior to commencing zanamivir and therefore zanamivir would not be expected to avert the need for hospitalisation. Since this patient remained hospitalised for 16 days and the number of hospital events was small, a sensitivity analysis excluding this one patient was performed to demonstrate the impact of one outlier on the cost-effectiveness ratio.

Cost Effectiveness

Table III reports the mean incremental costs and effects per patient. The incremental cost per patient treated with zanamivir was £44.94 including all hospitalisations. Excluding the hospitalisation costs for the one patient withdrawn from the study reduced the incremental cost to £21.67. Excluding all inpatient hospitalisation costs, treatment with zanamivir increased the cost of treatment per patient by £23.52. This suggests that the cost of zanamivir (£24.00) is the main driver behind the incremental cost, with offsets coming from the levels of additional healthcare contacts and antibacterial use.

The mean benefit was estimated to be 2.5 days in terms of normal activities gained, 2.0 symptom-free days and a 9% reduction in complications requiring antibacterial use. The ICER in the high-risk group (excluding hospitalisation costs) is therefore £9.50 per day of normal activities gained, £11.56 per symptom-free day gained and £262 per complication averted. Depending on whether the 1 outlying patient is included, the results showed ICERs ranging from £9 to £18 per day of normal activities gained. Figure 1 plots the results of the 5000 bootstrap resamples for time to return to normal activities (excluding inpatient hospitalisation costs).

Cost Utility

Results from the patient and GP assessments of baseline (non-influenza) and influenza health-states are displayed in table IV.

These agree well with the reported UK population norm of 0.825.[26] As the influenza health-state valuations were similar between the patients and GPs, the more conservative patient valuation has been used in the QALY calculations, in which the difference in utility between baseline and influenza states (0.883) is combined with the mean decrease in days to return to normal activities (2.48) and the incremental cost (£23.52). The result is a cost per QALY of £3920 (£7490 including hospitalisation costs). Since the cost per QALY is partly determined by the utility rate, a decrease in the utility difference between the influenza state and full health would lead to a proportional increase in the cost per QALY.

Cost-effectiveness acceptability curves for the cost per QALY are presented in figure 2. The results demonstrate that there is a 90% certainty that zanamivir would be cost effective (excluding inpatient costs) if the ceiling ratio for a QALY was £8000 and a 95% certainty that zanamivir would be cost effective if the ceiling ratio was £11 500 per QALY. The shape of the acceptability curves was replicated in each case using the parametric net benefit method, demonstrating that the distribution of ICERs was jointly normal.

Discussion

The comparator for zanamivir in this evaluation was placebo. Although amantadine is registered for prophylaxis and treatment of influenza A, it offers neither the scope for treatment (being only effective against influenza A) nor the widespread acceptance for it to be considered the standard of care. This is particularly so in acutely ill elderly patients whose renal function may not be known at the time of prescription. Vaccination is the primary method for managing influenza. Zanamivir is intended as an adjunct in vaccinated patients since the decision to administer a vaccine is based on patient risk factors and is made while the patient is asymptomatic before the influenza season begins. During the influenza season, some of those who have been vaccinated will develop influenza symptoms, as will some who have not been vaccinated. Since the consequences of influenza infection are more severe in those who have not been vaccinated, the associated costs would be expected to be higher in this group.

The analysis was performed on integrated patient-level data in order to compile as large a pool as possible of high-risk patients. This meant combining data from studies conducted across different countries and in different influenza seasons. Although a formal meta-analysis could estimate mean effects, the integration of patient level data was necessary to provide the cost and effect pairs for the bootstrap process. Extrapolation was necessary for those effect data that were censored. The extrapolation was limited to the length of the longest study (28 days). However, since there were more placebo patients than zanamivir patients whose symptoms were not alleviated at the end of studies, this assumption undervalues the effect of zanamivir.

Hospitalisations were not collected prospectively in the trials but were included as a sensitivity analysis based on SAE forms. Although there were more patients hospitalised in the high-risk zanamivir group, it would be expected that in a large enough population the significant reductions in complications for patients receiving zanamivir would in turn reduce the incidence of hospitalisations.

It is recognised that estimating utility for acute conditions has both measurement and evaluation

Table IV. Utility estimates from EQ-5D (EuroQoL instrument)[14] health-state questionnaire

Data source	n	Baseline	Influenza health-state (considering whole influenza illness)	Difference (95% confidence interval)	Influenza health-state (worst day)
Patients with influenza during past influenza season	21	0.817	–0.066	0.883 (0.697, 1.069)	–0.342
General practitioner assessment of hypothetical high-risk patient with influenza	8	0.720	–0.263	0.982 (0.875, 1.090)	Not collected

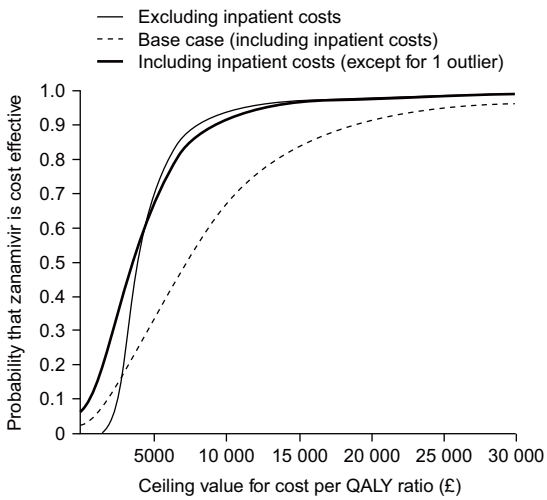

Fig. 2. Cost-effectiveness acceptability curve (nonparametric bootstrap method): cost (1999 values) per quality-adjusted life-year (QALY).

problems. However, Bala and Zarkin[27] maintain that these difficulties are more likely to bias against acute diseases. Since influenza is a self-limiting illness for the majority of patients, a patient's utility will vary during the course of the disease, being more severely impacted during the early days and then increasing as the patient begins to recover. To address this, the use of the utility estimate considering the entire period of the illness was used in the calculation rather than the value for the worst day.

Our results estimate the cost per QALY of zanamivir in the high-risk group to be £3920 (excluding inpatient costs). When compared with a recently compiled list of costs per QALY, the cost effectiveness of zanamivir compared favourably with that of other common pharmacological interventions.[28]

A preliminary cost-effectiveness analysis based upon the first completed zanamivir phase III study estimated the cost effectiveness of zanamivir in high-risk patients to be 11 715 Australian dollars (around £4600; 1998 values).[4] The present evaluation uses more comprehensive clinical trial data and a different methodology but shows a similar result.

This analysis was undertaken to estimate the cost effectiveness of zanamivir in high-risk patients under clinical trial conditions. Bootstrapping methodology was used to quantify the uncertainty around the point estimate of cost effectiveness. The effectiveness measures were based upon an observed diagnostic positivity rate of 71%. Additionally, the trials recruited only those patients who attended within 48 hours of developing symptoms. When implementing zanamivir treatment in practice, high diagnostic accuracy rates will depend upon the ability of doctors to detect true influenza. Clinical diagnosis of influenza in these studies has been shown to be 71% accurate. This relies solely on knowledge of common symptoms and signs of influenza, along with knowledge of local circulation of influenza virus. The impact on GPs of patients with influenza presenting outside 48 hours and patients with other respiratory infections is not evaluated in this analysis. The use of bootstrapping and cost-effectiveness acceptability curves address uncertainties in the clinical data and in decision-makers' willingness to pay for the benefits obtained. Uncertainties around the diagnostic rate and consultation patterns can only be reliably estimated once zanamivir is in routine use.

Conclusion

This economic evaluation reports a comprehensive analysis of the cost effectiveness of zanamivir in high-risk patients within the zanamivir clinical trial programme. The evaluation demonstrates that significant health benefits can be obtained with zanamivir therapy in high-risk patients, with cost-effectiveness point estimates (excluding inpatient costs) of £9.50 per day of normal activities gained, £11.56 per symptom-free day, £262 per complication averted and approximately £3900 per QALY.

Most economic evaluations present point estimates of cost effectiveness and may include some measure of CIs. The merits of these point estimates depend not only upon the uncertainty surrounding the estimates, but also decision-makers' willingness to pay for the benefits obtained. The cost-effectiveness acceptability curves presented address both these issues. We estimate that there is a 90% chance that the true cost effectiveness of

zanamivir lies below £8000 per QALY. The cost effectiveness of zanamivir in high-risk patients therefore compares well with the cost per QALY of other accepted pharmacological interventions.

Acknowledgements

We thank Andrew Briggs (Institute of Health Sciences, University of Oxford); Neil Dobson; Rebecca Warren; and Sophie Hall (GlaxoWellcome UK, Stockley Park, UK). A.D. Griffin and A.S. Perry conceived, designed and performed the economic evaluation. D.M. Fleming conducted the utility measurement in influenza patients and contributed to interpretation of clinical data. A.D. Griffin and A.S. Perry drafted the manuscript and D.M. Fleming critically reviewed it. All authors had final approval of the manuscript. D.M. Fleming serves as a consultant advisor to GlaxoWellcome in relation to their clinical trial programme for zanamivir. He has also received honoraria in respect of lecture presentations on influenza-related issues and for service on advisory boards to the pharmaceutical industry covering influenza vaccination and treatment.

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Correspondence and offprints: *Andrew Perry,* GlaxoWellcome R&D, Greenford Road, Greenford, Middlesex, UB6 0HE, UK. E-mail: asp90059@glaxowellcome.co.uk