NICE National Institute for Health and Care Excellence

NICE guidance

Amantadine, oseltamivir and zanamivir for the treatment of influenza

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA58.

1 Guidance

This guidance replaces 'Flu treatment – zanamivir (review) amantadine and oseltamivir' (NICE technology appraisal 58).

For details, see 'About this guidance'.

This guidance does not cover the circumstances of a pandemic, impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no community resistance.

1.1 Oseltamivir and zanamivir are recommended, within their marketing authorisations, for the treatment of influenza in adults and children if **all** the following circumstances apply:

- national surveillance schemes indicate that influenza virus A or B is circulating[1]
- the person is in an 'at-risk' group as defined in 1.2
- the person presents with an influenza-like illness and can start treatment within 48 hours (or within 36 hours for zanamivir treatment in children) of the onset of symptoms as per licensed indications.

1.2 For the purpose of this guidance, people 'at risk' are defined as those who have one of more of the following:

- chronic respiratory disease (including asthma and chronic obstructive pulmonary disease)
- chronic heart disease
- chronic renal disease
- chronic liver disease
- chronic neurological conditions

- diabetes mellitus.

  People who are aged 65 years or older and people who might be immunosuppressed are also defined as 'at-risk' for the purpose of this guidance.

1.3 The choice of either oseltamivir or zanamivir in the circumstances described in 1.1 should be made after consultation between the healthcare professional, the patient and carers. The decision should take into account the patient's preferences regarding drug delivery and potential adverse effects and contraindications. If all other considerations are equal, the drug with the lowest acquisition cost should be offered.

1.4 During localised outbreaks of influenza-like illness (outside the periods when national surveillance indicates that influenza virus is circulating in the community), oseltamivir and zanamivir may be offered for the treatment of influenza in 'at-risk' people who live in long-term residential or nursing homes. However, these treatments should be offered only if there is a high level of certainty that the causative agent in a localised outbreak is influenza (usually based on virological evidence of influenza infection in the initial case).

1.5 Amantadine is not recommended for the treatment of influenza.

[1] The Health Protection Agency in England (and the equivalent bodies in Wales and Northern Ireland) uses information from a range of clinical, virological and epidemiological influenza surveillance schemes to identify periods when there is a substantial likelihood that people presenting with an influenza-like illness are infected with influenza virus.

2 Clinical need and practice

2.1 Influenza is an acute infection of the respiratory tract caused by the influenza A and B viruses. The symptoms of influenza include fever, cough, sore throat, myalgia and headache. These symptoms are not specific to influenza, and can be caused by other viruses (such as respiratory syncytial virus) which can present as an 'influenza-like illness'. Diagnosis of influenza can only be confirmed by laboratory testing, although the probability that an influenza-like illness is caused by influenza is higher if influenza is known to be circulating and if a person has a high fever. The symptoms of influenza-like illness can be different in infants and children and may include fatigue, irritability, diarrhoea and vomiting. Influenza infection is usually self-limiting and lasts for 3–4 days, with some symptoms persisting for 1–2 weeks. The severity of the illness can vary from asymptomatic infection to life-threatening complications. The most common complications are secondary bacterial infections such as otitis media, pneumonia and bronchitis. In the UK, the average number of deaths attributed directly to influenza is approximately 600 in non-epidemic years and between 12,000 and 13,800 deaths in epidemic years.

2.2 Influenza occurs in a seasonal pattern with epidemics in the winter months, typically between December and March. The illness is highly contagious and is spread from person to person by droplets of respiratory secretions produced by sneezing and coughing. Influenza activity is monitored through surveillance schemes, which record the number of new GP consultations for influenza-like illness per week per 100,000 population. In 1997, normal seasonal activity in England was defined as 30–200 consultations, with greater than 200 defined as an epidemic. In Wales, the corresponding figures are 25–100, and greater than 400. In addition, there are virological monitoring schemes based on the isolation of the virus from clinical specimens. 'Normal seasonal activity', as measured by these surveillance schemes, corresponds to the term 'circulating' in 'Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza' (NICE technology appraisal guidance 58). Accurate monitoring of influenza activity requires analysis of clinical, virological and epidemiological information.

2.3 The management of influenza is supportive and consists of relieving symptoms while awaiting recovery. Complications require specific management, and antibiotics are used for secondary bacterial infections. Vaccination has been established as the first-line intervention to prevent influenza and its complications. In the UK, the Department of Health currently recommends that people who are at risk of influenza infection or complications are vaccinated at the beginning of each winter. These include people with chronic respiratory, heart, renal, liver or neurological disease, people with diabetes, people who are immunosuppressed, people aged 65 and older, people who work or live in residential care facilities, carers of 'at-risk' people, healthcare and other essential workers and poultry workers.

2.4 Antiviral drugs are also used for the prevention of influenza. They may be given to people who have been in contact with a person with influenza-like illness (post-exposure prophylaxis) and may be given in the absence of known contact when it is known that influenza is circulating in the community (seasonal prophylaxis). When antiviral drugs are given for seasonal prophylaxis, they are used for longer periods to cover the duration of the influenza season. Seasonal prophylaxis may be considered in exceptional situations such as an antigenic mismatch between circulating strains of the influenza virus and that used for vaccination, which would mean that 'at-risk' people are not effectively protected by vaccination. Prophylaxis may also be used to control outbreaks of influenza within a residential community. A review on the use of antiviral drugs for the prophylaxis of influenza (NICE technology appraisal guidance 158) recommends oseltamivir and zanamivir for post-exposure prophylaxis only.

3 The technologies

Amantadine

3.1 Amantadine (Lysovir, Symmetrel, Alliance Pharmaceuticals) acts against influenza A virus by blocking viral replication. It has a UK marketing authorisation for the treatment of people who have signs and symptoms of infection caused by influenza A virus. The summary of product characteristics (SPC) states that treatment should be started as early as possible, and within 48 hours of symptom onset. The recommended dosage of amantadine is 100 mg daily for 4–5 days. Amantadine is administered orally as syrup (Symmetrel) or 100-mg capsules (Lysovir) for the treatment of influenza.

3.2 The adverse effects associated with amantadine are often mild and transient. The most commonly reported effects are gastrointestinal disturbances such as anorexia and nausea, and central nervous system effects such as loss of concentration, dizziness, agitation, nervousness, depression, insomnia, fatigue, weakness and myalgia. Central nervous system effects are most common in older people. For full details of adverse effects and contraindications, see the SPC.

3.3 Amantadine costs £2.40 for five capsules (100 mg each), £4.80 for 14 capsules and £5.55 for 150 ml syrup (50 mg/5 ml) (excluding VAT; 'British national formulary' [BNF] edition 55). Costs may vary in different settings because of negotiated procurement discounts.

Oseltamivir

3.4 Oseltamivir (Tamiflu, Roche Products) is a neuraminidase inhibitor that is active against influenza A and B viruses. It prevents viral release from infected cells and subsequent infection of adjacent cells. It has a UK marketing authorisation for the treatment of influenza in people 1 year of age or older who present with symptoms typical of influenza, when influenza virus is circulating in the community. The SPC states that

treatment should be started as soon as possible within the first 48 hours of the onset of influenza symptoms. The recommended dosage of oseltamivir for adolescents (13–17 years of age) and adults is 75 mg twice daily for 5 days. For infants older than 1 year and children 2–12 years of age, the recommended dose of oseltamivir is adjusted according to body weight. Oseltamivir is given orally as syrup or capsules.

3.5 Adverse effects associated with oseltamivir include gastrointestinal symptoms, bronchitis and cough, dizziness and fatigue and neurological symptoms such as headache, insomnia and vertigo. Skin rashes and allergic reactions and, rarely, disorders of the hepatobiliary system have been reported. Convulsions and neuropsychiatric disorders, mainly in children and adolescents, have also been reported but a causal link has not been established. For full details of adverse effects and contraindications, see the SPC.

3.6 Oseltamivir costs £16.36 for a 5-day course for an adult (excluding VAT; BNF edition 55). Costs may vary in different settings because of negotiated procurement discounts.

Zanamivir

3.7 Zanamivir (Relenza, GlaxoSmithKline) is a neuraminidase inhibitor that is active against influenza A and B viruses. It prevents viral release from infected cells and subsequent infection of adjacent cells. It has a UK marketing authorisation for the treatment of influenza in people older than 5 years who present with symptoms typical of influenza, when influenza is circulating in the community. The SPC states that treatment should begin as soon as possible, within 48 hours of symptom onset for adults and within 36 hours of symptom onset for children. The recommended dosage of zanamivir for people older than 5 years is 10 mg twice daily for 5 days. Zanamivir is taken by oral inhalation, using a Diskhaler device.

3.8 Adverse effects associated with zanamivir are rare. They include bronchospasm and allergic phenomena. For full details of adverse effects and contraindications, see the SPC.

3.9 The price of zanamivir was reduced during the course of the appraisal from £24.55 (excluding VAT; BNF edition 55) to £16.36 (excluding VAT; BNF edition 56) for a 5-day course. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

4.1.1 The Assessment Group performed a systematic review to identify randomised controlled trials (RCTs) evaluating the clinical effectiveness of amantadine, oseltamivir and zanamivir compared with each other, placebo or with best symptomatic care. Studies included were conducted in people who presented with symptoms typical of influenza, whether influenza was reported as circulating in the community or not. The population was divided into the following categories: otherwise healthy adults; 'at-risk'; older people; children; and 'mixed' populations. Twenty-nine RCTs were identified by the systematic review. There was no new evidence on the clinical effectiveness of amantadine published after the review of the evidence for TA 58. No RCTs that directly compared zanamivir and oseltamivir were included; a Bayesian indirect comparison using placebo as a common comparator was conducted. The trials generally compared zanamivir or oseltamivir with placebo. The background circulating levels of influenza and the influenza vaccination rate in the trials were often not reported clearly. Levels of viral resistance were often not measured, but when reported were low.

4.1.2 In most RCTs, the effectiveness of the antiviral drugs was measured in terms of time to alleviation of symptoms (a composite outcome) and time to return to normal activities. Adverse events and complications were also reported, the latter generally in terms of reductions in antibiotic usage. Analyses were reported for the ITT population (intention to treat; representative of the entire population recruited in the trials) and ITTI population (intention to treat, confirmed as being influenza positive) wherever possible.

4.1.3 Evidence was submitted by consultees that there has been a decline in the rates of GP consultations for acute respiratory illnesses over the past

25 years. This has resulted in the lowering of the threshold levels of the surveillance schemes. In addition, it was stated that the influenza season as defined by the surveillance schemes does not correspond exactly to the period during which the virus is circulating in the community as indicated by virological monitoring. It was also apparent that outbreaks of influenza occur within localised areas, especially in residential care settings, outside of the influenza season.

Oseltamivir

4.1.4 The Assessment Group's systematic review identified 16 RCTs. Eight of these had been considered for TA 58 and eight were new studies that had been published since the review of evidence for TA 58. Two of the included studies recruited mixed populations, seven recruited only healthy adults, two recruited from general 'at-risk' populations, two recruited only children and three recruited only older people. Follow-up periods ranged from 10 to 28 days.

4.1.5 Most of the included studies reported time to alleviation of symptoms and the Assessment Group conducted meta-analyses by population subgroup and by whole population. Overall, oseltamivir reduced the median time to alleviation of symptoms by 0.68 days (95% confidence interval [CI] 0.41 to 0.95) and 0.95 days (95% CI 0.50 to 1.39) in the ITT (n = 5036) and ITTI (n = 2541) analyses, respectively. The reduction in median time to alleviation of symptoms associated with oseltamivir treatment ranged from 0.41 days (older people) to 0.88 days (healthy and 'at-risk' children) in the ITT analyses and from 0.43 days ('at-risk' children) to 1.50 days (healthy children) in the ITTI analyses.

4.1.6 Most of the included studies also reported time to return to normal activity and the Assessment Group conducted meta-analyses by population subgroup and by whole population. Overall, oseltamivir reduced the median time to return to normal activity by 1.32 days (95% CI 0.91 to 1.73) and 1.51 days (95% CI 1.01 to 2.02) in the ITT (n = 2754) and ITTI (n = 3013) analyses, respectively. The reduction in median time to return to normal activity associated with oseltamivir treatment ranged from 1.25 days (healthy children) to 4.09 days (older people) in the ITT analyses and from 0.50 days ('at-risk' children) to 3.07 days (older

people) in the ITTI analyses.

4.1.7 Alleviation of fever was reported in a few studies. Because the studies that reported alleviation of fever were generally conducted in healthy or mixed populations, meta-analyses were not presented by population category. All of the trials showed a reduction in the time to alleviation of fever. Overall, oseltamivir reduced the median time to alleviation of fever by 18.7 hours in the ITT population (95% CI 9.70 to 27.8, n = 1177) and 24.4 hours in the ITTI population (95% CI 17.2 to 31.6, n = 1720).

4.1.8 The data on complications were sparse and only the use of antibiotics was significantly reduced for those who received oseltamivir compared with placebo (ITTI population, odds ratio [OR] 0.62, 95% CI 0.46 to 0.83 for antibiotic use, n = 2175). Across all trials, there was no evidence of a difference in the incidence of overall, serious or drug-related adverse effects between oseltamivir and placebo. Among the nine trials that reported mortality, there was a single death in the placebo arm of a trial in an 'at-risk' population; it was not clear whether this death was associated with influenza.

Zanamivir

4.1.9 The Assessment Group's systematic review identified 13 RCTs. Seven of these had been considered for TA 58 and six were new studies that had been published since the review of evidence for TA 58. Five of the studies recruited a mixed population (for which data on symptoms for healthy and 'at-risk' adults were available separately), three recruited only healthy adults, two recruited from general 'at-risk' populations, two recruited only children and one recruited only older people. The follow-up period ranged from 5 to 29 days.

4.1.10 Most of the included studies reported time to alleviation of symptoms and the Assessment Group conducted meta-analyses by population subgroup and by whole population. Overall, zanamivir reduced the median time to alleviation of symptoms by 0.71 days (95% CI 0.41 to 1.01) and 1.07 days (95% CI 0.74 to 1.39) in the ITT (n = 4538) and ITTI (n = 2865) analyses, respectively. The reduction in the median time to alleviation of symptoms associated with zanamivir treatment ranged from

0.57 days (healthy adults) to 2.00 days ('at-risk' children) in the ITT analyses and from 0.96 days (healthy adults) to 3.75 days ('at-risk' children) in the ITTI analyses.

4.1.11 Most of the included studies also reported time to return to normal activity and the Assessment Group conducted meta-analyses by population subgroup and by whole population. Overall, zanamivir reduced the median time to return to normal activity by 0.44 days (95% CI 0.05 to 0.84) and 0.71 days (95% CI 0.19 to 1.24) in the ITT (n = 4053) and ITTI (n = 2877) analyses, respectively. The reduction in median time to return to normal activity associated with zanamivir treatment ranged from 0.37 days (healthy adults) to 1.07 days ('at-risk' adults) in the ITT analyses and from 0.39 days (healthy adults) to 2.50 days ('at-risk' children) in the ITTI analyses.

4.1.12 Alleviation of fever was reported in four studies but only one reported any measure of variance, so meta-analyses could not be conducted. Across the studies that reported this outcome (n = 1539), the median time to alleviation of fever was reduced by between 0.0 and 0.5 days for zanamivir compared with placebo.

4.1.13 Although the data on complications were sparse, the incidence of overall complications and the use of antibiotics were significantly reduced for those who received zanamivir compared with placebo (ITTI populations, n = 2629, OR 0.77, 95% CI 0.65 to 0.92, p = 0.004 for overall complications; OR 0.79, 95% CI 0.63 to 0.99, p = 0.04 for antibiotic use). Across all trials, treatment with zanamivir significantly reduced the incidence of overall adverse events compared with placebo (OR 0.85, 95% CI 0.75 to 0.96, p = 0.007, n = 5430) but there was no evidence of a difference in the incidence of drug-related adverse events. Very few serious adverse events were reported and there were no deaths in any of the seven zanamivir trials that reported mortality.

Indirect comparison of oseltamivir and zanamivir

4.1.14 The Assessment Group identified one direct comparison of zanamivir and oseltamivir but excluded this trial because it did not report usable outcome data. Therefore, the Assessment Group performed an indirect

comparison of zanamivir and oseltamivir using a multi-parameter Bayesian approach. The probabilities that each treatment was 'best' were calculated for the following population subgroups: otherwise healthy adults; otherwise healthy children; and an 'at-risk' group that combined 'at-risk' children, 'at-risk' adults and older people (owing to few data). All analyses were presented with associated 95% credibility intervals (CrI). A 95% Bayesian credibility interval means that, given the data, there is a 95% probability that the random variable lies within the interval.

4.1.15 Across all analyses, point estimates suggested that either oseltamivir or zanamivir was more effective than placebo, but not all analyses were statistically significant. There was variation across population subgroups as to whether zanamivir or oseltamivir had a higher probability of being most effective. In all of the analyses, the median time to alleviation of symptoms and return to normal activity was shorter in the ITTI analyses than the ITT analyses. In the ITTI analyses, zanamivir treatment compared with placebo reduced the days to alleviation of symptoms by 1.3 (95% CrI 0.30 to 2.96) and 4.7 (95% CrI 1.98 to 9.44) for healthy adults and the 'at-risk' group, respectively. Similar analyses for oseltamivir treatment compared with placebo gave reductions of 2.08 (95% CrI 0.73 to 4.34) and 2.63 (95% CrI 0.38 to 6.53) days for healthy adults and healthy children, respectively. The ITTI analyses for zanamivir compared with placebo for healthy children gave a reduction of 1.77 days (95% CrI –0.41 to 5.10) and for oseltamivir compared with placebo in the 'at-risk' group gave a reduction of 1.56 days (95% CrI –0.78 to 4.66), but in both cases the credibility intervals included zero. In ITTI analyses for days to return to normal activities, zanamivir treatment compared with placebo gave reductions of 1.65, 5.97 and 2.25 for healthy adults, the 'at-risk' group and healthy children, respectively. In the ITTI analyses, compared with placebo oseltamivir treatment reduced the days to return to normal activity by 2.64, 1.98 and 3.34 for healthy adults, the 'at-risk' group and healthy children, respectively.

4.2 Cost effectiveness

4.2.1 The Assessment Group identified 21 cost-effectiveness studies that assessed amantadine, oseltamivir or zanamivir for the treatment of influenza. The manufacturer of oseltamivir (Roche Products) also

provided a de novo economic model. No cost-effectiveness analyses were submitted by the manufacturers of amantadine or zanamivir. Seven of the identified cost-effectiveness studies were conducted from the perspective of the NHS (including the assessment for the original appraisal TA 58 and the current submission from Roche Products).

4.2.2 The decision-tree model developed by the Assessment Group for TA 58 was designed to compare amantadine, oseltamivir and zanamivir with usual care for the treatment and prophylaxis of influenza. The following four separate groups were considered: otherwise healthy adults; high-risk ('at-risk') adults; children; and older people in residential care. For each of the population groups, amantadine compared with usual care had the lowest incremental cost-effectiveness ratios (ICERs), which ranged from £4535 to £6190 per quality-adjusted life-year (QALY) gained. However, the Appraisal Committee for the original appraisal TA 58 was unable to accept that the clinical effectiveness of amantadine was sufficiently proven and so it did not recommend amantadine for the treatment of influenza A. The ICERs for oseltamivir compared with usual care ranged from £19,015 to £22,502 per QALY gained. The ICERs for zanamivir compared with usual care ranged from £16,819 to £31,529 per QALY gained.

4.2.3 Of the five other studies conducted from the UK NHS perspective, two compared zanamivir with usual care in both healthy and 'at-risk' adults, two compared oseltamivir with usual care in healthy children and healthy adults, and one compared oseltamivir, zanamivir and usual care in healthy adults. The estimated ICERs for zanamivir compared with usual care ranged from £7490 to £54,000 per QALY gained for 'at-risk' adults and £65,000 per QALY gained for otherwise healthy adults. The estimated ICERs for oseltamivir compared with usual care ranged from oseltamivir being dominant to £11,173 per QALY gained for healthy children, and £225 to £5600 for adults per QALY gained. In the only comparison of oseltamivir with zanamivir (in healthy adults), zanamivir was dominated (that is, zanamivir was estimated to be more costly and less effective than oseltamivir).

Manufacturer's model

4.2.4 The current submission from the manufacturer of oseltamivir (Roche Products) included a decision-tree economic model that estimated the cost effectiveness of oseltamivir compared with zanamivir and usual care for the treatment of influenza, using separate pairwise comparisons. The model considered the following population subgroups separately: otherwise healthy adults; 'at-risk' adults (including older adults); otherwise healthy children aged 1–12 years; and otherwise healthy children aged 1–5 years. The model started when a patient presented to a GP with an influenza-like illness when influenza was reported to be circulating in the community. The probability that the illness was influenza was assumed to be 31% in all populations modelled. For the comparison of oseltamivir with zanamivir it was assumed that the drugs are equally effective. A cost-minimisation approach was used and the total cost of a course of zanamivir was assumed to be £0.19 higher than that of oseltamivir. The health state utility for influenza-like illness without complication was assumed to be 0.840; this was taken from Harvard utility scores and was assumed not to differ between populations. Zanamivir and oseltamivir treatment was assumed to be associated with an improved utility of 0.937; this improved utility was derived from the oseltamivir clinical trials. The resource-use data cover costs associated with GP visits, diagnostic tests, antibiotic treatments and hospital visits.

4.2.5 The comparison of oseltamivir with usual care for the treatment of influenza produced base-case ICERs of £5452 per QALY gained for healthy adults, £5992 per QALY gained for healthy children aged between 1 and 12 years, £4687 per QALY gained for healthy children aged between 1 and 5 years and £652 for 'at-risk' adults. For all populations, zanamivir was dominated by oseltamivir (that is, oseltamivir was less costly and more effective than zanamivir). The model was sensitive to the changes in assumptions of the probability that an influenza-like illness was true influenza and the probability that patients presented to a GP within 48 hours.

Assessment Group model

4.2.6 The Assessment Group conducted an independent economic assessment. The model was used to develop incremental estimates of the cost effectiveness of oseltamivir and zanamivir for the treatment of influenza compared with usual care without antiviral treatment. The Assessment Group did not develop estimates of the cost effectiveness of amantadine for the treatment of influenza because it is not widely used and was not recommended for use in TA 58. The decision-tree model evaluated costs from an NHS and personal social services perspective. A single influenza season was modelled; however, a lifetime horizon was used to account for any reductions in life expectancy. The model started when a patient presented to a healthcare professional with an influenza-like illness and was considered suitable for treatment with either oseltamivir or zanamivir (according to the respective UK marketing authorisations of each antiviral drug). Cost-effectiveness estimates for influenza treatment were presented for the following population groups: otherwise healthy children (aged 1–14 years); 'at-risk' children (aged 1–14 years); otherwise healthy adults (aged 15–64 years); 'at-risk' adults (aged 15–64 years) and the 'elderly' (defined as adults older than 65 years). The model assumed that oseltamivir and zanamivir would be prescribed only when influenza was known to be circulating in the community, based on national surveillance schemes (this was assumed to be defined as 30 new GP consultations for influenza-like illness per 100,000 population).

4.2.7 The probability that an influenza-like illness is true influenza was derived from national surveillance data provided by the Royal College of General Practitioners. The average probability that influenza-like illness was influenza was 0.495. However, calculating this for the separate age groups resulted in a probability of 0.56 (CrI 0.26 to 0.79) in people younger than 15 years and 0.41 (CrI 0.21 to 0.66) in people aged 15 years and over.

4.2.8 The effectiveness of oseltamivir and zanamivir was derived from the overall duration of symptoms (that is, based on time to alleviation of symptoms) for the different subgroups in the model. These were taken directly from the mean ITTI results from the indirect Bayesian multi-

parameter evidence synthesis model. The same mean duration of symptoms was applied to each of the separate 'at-risk' populations considered in the economic model. The relative effectiveness estimates from the ITTI populations were assumed to be independent of previous vaccination or prophylactic use of antivirals. The relative effectiveness of oseltamivir and zanamivir was assumed to be the same for both influenza type A and B. Both treatments were considered to be effective only in people with true influenza.

4.2.9 The Assessment Group used the duration of symptoms as the basis for estimating the potential QALY gains associated with the reduction in symptom duration reported for oseltamivir and zanamivir compared with usual care. A systematic search of the literature was undertaken to identify suitable health-related quality of life data. Although the Assessment Group identified some studies, none presented comparable estimates for different risk groups and there were limitations in the methods used. Therefore, the utility values were based on those applied in TA 58. The data used in TA 58 were derived from the transformation of visual analogue scale (VAS) data reported in some of the oseltamivir trials into time trade-off utilities over a 21-day period. These data were then augmented with symptom duration estimates from the full range of RCTs identified in the current clinical effectiveness review. Separate values were reported for otherwise healthy adults and 'at-risk' adult populations. In the base-case analyses, the average quality of life decrement over the duration of influenza illness applied to healthy populations was between 0.4 and 0.5. The corresponding figure for 'at risk' populations was between 0.5 and 0.6. The Assessment Group also noted that if treatment of influenza shortens the duration of symptoms by reducing them at the end rather than the beginning of the illness, then the overall average decrement would be reduced to between 0.22 and 0.23 for healthy populations and 0.45 for 'at risk' populations. Adverse effects from oseltamivir and zanamivir were assumed to be mild and self-limiting and were assumed not to impact on a person's health-related quality of life.

4.2.10 The model then assumed that all people with influenza-like illness (whether influenza or not) had a probability of developing a complication. Estimates of the baseline probabilities of developing each complication

(and subsequent mortality) were derived separately for each subgroup from data reported in a large UK population-based study and ranged from 7.55% (healthy adults) to 17.59% ('at-risk' children). In the model, it was possible for a person to experience more than one complication; the probability of this was estimated for each person in each subgroup. Estimates of how effective the different treatments were at reducing the incidence of complications were based on the relative risk of antibiotic use. The relative risks for complications with zanamivir compared with placebo were 0.71 (95% CI 0.34 to 1.45), 0.74 (95% CI 0.35 to 1.57) and 0.78 (95% CI 0.45 to 1.35) for healthy adults, the 'at-risk' group and children, respectively. The relative risks for complications with oseltamivir compared with placebo were 0.57 (95% CI 0.24 to 1.35), 0.69 (95% CI 0.50 to 0.93) and 0.56 (95% CI 0.36 to 0.87) for the healthy adults, the 'at-risk' group and children, respectively. The quality of life estimates were decreased according to type of complication.

4.2.11 Likelihood of hospitalisation as a result of each type of complication was also included in the model; however, only complicated cases were assumed to lead to hospitalisation and death. Premature death as a result of influenza was assumed to occur only following a secondary complication (irrespective of whether a person was hospitalised). Given limitations in the evidence base, it was assumed that hospitalisation occurred only as a result of respiratory tract infections. The model assumed that all people who develop a complication face a subsequent probability of mortality that varies only by population subgroup, not by treatment strategy or previous hospitalisation. Mortality was assumed to have no cost implication, but resulted in loss of potential QALYs. In each population age group (children, adults and older people), the expected age of death from complications related to an influenza-like illness was derived from data from national statistics reporting influenza deaths by age group.

4.2.12 The acquisition cost of oseltamivir (£16.36) was based on the BNF (edition 55) list price, with identical estimates applied for zanamivir based on the revised price (see section 3.9). The costs associated with people developing complications as a result of influenza or influenza-like illness were also included. These costs included visits to a healthcare provider for treatment, antibiotics and hospitalisation.

4.2.13 A total of 12 scenario analyses were investigated by the Assessment Group. These analyses included investigation of assumptions such as those made about complications, the probability that an influenza-like illness was true influenza and the relative efficacy of oseltamivir and zanamivir.

4.2.14 In base-case results, for each population the ICER for both oseltamivir and zanamivir (relative to usual care) was less than £20,000 per QALY gained, and across the separate populations ranged from £562 to £7035 per QALY gained. In healthy children and healthy adults oseltamivir dominated zanamivir, with ICERs of £7035 and £5521 per QALY gained, respectively. In 'at-risk' children, 'at-risk' adults and older people zanamivir extendedly dominated oseltamivir (that is, the ICER for oseltamivir treatment is higher than that of zanamivir and usual care and is therefore ruled out on the basis of extended dominance). The ICERs were £1752 per QALY gained for 'at-risk' children, £2270 for 'at-risk' adults and £562 for older people. At a willingness to pay threshold of £20,000 per QALY gained, the probability that zanamivir was cost effective ranged from 23% (healthy children) to 90% ('at-risk' adults) and the probability that oseltamivir was cost effective ranged from 10% ('at-risk' adults) to 77% (healthy adults). The probability that usual care was cost effective at the same threshold was 0% (healthy adults, 'at-risk' adults, older people) to 4% (healthy children).

4.2.15 Across the 12 scenario analyses performed by the Assessment Group, the overall conclusions and ICERs in the 'at-risk' populations were generally consistent. The ICERs appeared more sensitive in the otherwise healthy populations. The base-case estimates of the ICERs of oseltamivir and zanamivir compared with usual care in the healthy populations were sensitive to the following key assumptions: the exclusion of hospitalisation and mortality benefits with antiviral treatment (these were included in the base case and ICERs in the scenario analyses ranged up to £13,985 per QALY gained); a reduction in the probability that an influenza-like illness is true influenza (this was 0.41 for adults and 0.56 for children in the base case and the ICERs in the scenario analyses ranged up to £47,573 per QALY gained, and up to £48,390 per QALY gained if hospitalisation and mortality benefits were excluded); increases in consultations with healthcare providers combined with decreases in

the probability that an influenza-like illness is influenza (ICERs in the scenario analyses ranged up to £13,959 per QALY gained, and up to £28,950 per QALY gained if hospitalisations and mortality benefits were excluded); and reductions in the decrements in quality of life associated with influenza (ICERs in the scenario analyses ranged up to £29,115 per QALY gained, and up to £59,684 per QALY gained if hospitalisation and mortality benefits were excluded).

4.2.16 The Assessment Group conducted additional scenario analyses for healthy children and healthy adults, which combined the following parameters:

- exclusion of hospitalisation and mortality benefits
- an increase in GP consultations (between 5 and 15%)
- a decrease in the probability that an influenza-like illness is true influenza (between 5 and 15%)
- a smaller decrement in quality of life associated with influenza of 0.2 (this value reflects the estimate detailed in section 4.2.9 corresponding to reduction in the duration of symptoms being at the end of the illness. The sensitivity analyses of quality of life decrements were explored in increments of 0.1).

  These scenario analyses resulted in ICERs that ranged from £21,003 to £31,491 per QALY gained for healthy children and from £39,862 to £65,607 per QALY gained for healthy adults.

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of amantadine, oseltamivir and zanamivir, having considered evidence on the nature of the condition and the value placed on the benefits of amantadine, oseltamivir and zanamivir by people with influenza, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.3.2 The Committee understood that influenza causes a wide spectrum of

respiratory illness of varying severity, and can lead to a number of potentially serious complications, especially in certain 'at-risk' groups. The Committee discussed the definition of 'at-risk' groups for whom treatment might be particularly suitable and decided that they would be best defined in the same way as for the current recommendations for vaccination. From the outset the Committee was of the view that vaccination has been established as the first-line intervention to prevent influenza and its complications, and was mindful that the use of antiviral treatments should not in any way detract from efforts to ensure that all eligible people are vaccinated at the beginning of each influenza season.

4.3.3 The Committee noted that the surveillance scheme used in the NHS to determine levels of influenza activity in the community was based on clinical consultations, but that influenza activity as defined by the threshold levels of these consultation rates did not always coincide with laboratory-based virological evidence. The Committee understood that the Health Protection Agency in England and similar organisations in Wales and Northern Ireland use information from a range of clinical, virological and epidemiological influenza surveillance schemes to identify when influenza is circulating in the community. The Committee heard from clinical specialists that the threshold levels are not suitable for defining when antiviral treatments would be most efficacious because they do not accurately identify periods when influenza, as opposed to influenza-like illness, is circulating.

4.3.4 The Committee considered the evidence for effectiveness of amantadine and noted that no new evidence on either the clinical or cost effectiveness of amantadine for the treatment of influenza had been published since the review of the evidence for TA 58. The Committee concluded that it had no basis on which to change the recommendations on the use of amantadine from the original appraisal (TA 58). Therefore amantadine is not recommended for the treatment of influenza.

4.3.5 The Committee then reviewed the evidence on the clinical effectiveness of oseltamivir and zanamivir for the treatment of influenza. The Committee noted that in all of the population subgroups, treatment with either antiviral drug was associated with reductions in the average duration of symptoms compared with placebo, although the difference

was not statistically significant in all subgroups. The Committee acknowledged that the reduction in duration of symptoms was generally greater for the 'at-risk' population compared with healthy populations. The Committee heard from clinical experts that this increased reduction in duration of symptoms for the 'at-risk' group was plausible for a number of reasons. It is likely that people in 'at-risk' groups would have a longer duration of illness, and would therefore be more likely to benefit from antiviral treatment. There is also clinical rationale to suggest that people in 'at-risk' groups could also suffer from exacerbations of underlying conditions as a result of influenza. This could increase the duration and severity of influenza symptoms, which would mean an increased potential benefit from antiviral treatments. These exacerbations might also lead to a person not recovering completely, and future influenza infections and subsequent exacerbations being more frequent. The Committee concluded that there is evidence indicating clinical effectiveness of antiviral drugs in a wide range of clinical settings, but that their use is of greatest clinical importance for people in 'at-risk' groups.

4.3.6 The Committee noted that the probabilities for each antiviral drug being the 'best' treatment also differed according to population subgroup. The Committee discussed these results with clinical experts. The Committee was not persuaded that there was any plausible biological explanation for these observed differences. The Committee considered that the data were too sparse and uncertain to allow for any clear distinctions between the antiviral treatments to be made on the basis of clinical efficacy between different populations. The Committee concluded that oseltamivir and zanamivir are both clinically effective treatments for influenza, particularly for those people in 'at-risk' groups.

4.3.7 The Committee considered the evidence on adverse events associated with oseltamivir and zanamivir. The Committee was aware that very sparse adverse event data were reported in the included RCTs. However, it noted that no significant differences between the antiviral treatments compared with placebo were reported.

4.3.8 The Committee considered the structure of the economic models used to generate cost-effectiveness estimates for oseltamivir and zanamivir for

the treatment of influenza. The Committee was aware that the models submitted by the manufacturer and the Assessment Group were not dynamic models. That is, the models did not account for effects of influenza treatment in reducing transmission of infection, the development of 'herd immunity', the potential for the development of drug resistance and the effect of treatment of influenza-like illness on attack rates. The Committee appreciated that some aspects of this approach to modelling additional benefits could improve the cost effectiveness of the antiviral agents but that there were potential disadvantages that would make treatment less cost effective. The Committee was also aware that dynamic models were technically complicated and that the current evidence would not have been sufficient to support this modelling approach. The Committee concluded that the evidence available from the submitted models was an appropriate basis on which to make a decision and that on balance an alternative dynamic modelling approach would not change its overall conclusions.

4.3.9 The Committee then reviewed the cost-effectiveness estimates of oseltamivir and zanamivir as submitted by the manufacturer of oseltamivir and the Assessment Group. In particular, the Committee considered the key inputs in the models were the probability that an influenza-like illness is true influenza and complication rates following influenza infection and subsequent related hospitalisation and mortality.

4.3.10 The Committee first considered the different estimates of the probability that an influenza-like illness is true influenza. The Committee noted that the probability used in the manufacturer's model was lower than that used in the Assessment Group model (for which different probabilities were used according to age group). The Committee was aware that the confidence intervals surrounding the probability estimates for different population subgroups used in the Assessment Group model were wide and overlapped with one another. The Committee heard from clinical experts that the probability of an influenza-like illness being true influenza in children was likely to be lower than that assumed in the Assessment Group model because of increased difficulties in diagnosis in children and the probability of other conditions such as respiratory syncytial virus, which can present as influenza-like illness. The

Committee thought that this was particularly likely for otherwise healthy children and concluded that the estimate of 56% (influenza-like illness is true influenza) was too high and should be more closely aligned to that of adults (that is, 41%).

4.3.11 The Committee considered whether the vaccination status would affect the probability that a person presenting with an influenza-like illness would have true influenza. The Committee considered that this would depend on a number of factors, including whether the vaccine was appropriately matched to the currently circulating strain of influenza virus and whether sufficient time had elapsed since vaccination to ensure it was effective. The Committee noted that there were insufficient data on which to inform differential considerations on the basis of vaccination status. Therefore the Committee concluded that any recommendation on the use of antiviral drugs would not distinguish between vaccinated and non-vaccinated people.

4.3.12 The Committee then discussed whether increases in GP consultation rates (for example, as a result of a positive recommendation for the use of antiviral drugs) could result in more people presenting to a healthcare provider with an influenza-like illness that was not true influenza. The Committee heard from clinical experts that this was plausible. The Committee was also aware that current surveillance schemes are based in part on the number of GP consultations, and increases in consultation rates could lead to an apparent increase in influenza prevalence and thus reduction in the positive predictive value of influenza diagnoses. The Committee considered that such a scenario was more probable in healthy populations. The Committee concluded that for healthy populations increases in GP consultation rates would lead to decreases in the probabilities that an influenza-like illness was true influenza. The Committee was also aware that there would be extra costs associated with an increase in GP consultation rates. Therefore the Committee concluded that the base-case ICERs for these groups would be underestimates if a positive recommendation were given.

4.3.13 The Committee considered the effects of oseltamivir and zanamivir treatment on complication rates associated with influenza. The Committee noted that the economic model provided by the Assessment

Group included complication rates based only on reductions in antibiotic use in the absence of more direct data. The Committee was aware that there may be additional, alternative, approaches to measuring complication rates and that there were wide confidence intervals and uncertainty in the relative reduction rates in antibiotic use, particularly for healthy adults and children. The Committee also considered that the lower severity and duration of influenza symptoms, as may occur in healthy populations compared with 'at-risk' populations as discussed in section 4.3.5, could lead to a lower incidence of complications and subsequent hospitalisations.

4.3.14 The Committee considered the effects of influenza on health-related quality of life. In the Assessment Group base case, an average quality of life decrement had been applied across the duration of an episode of influenza illness. The Committee noted that influenza is generally associated with worse disutility at the beginning rather than at the end of the illness. The Committee considered that it is more plausible that a reduction in symptoms arising from treatment would occur at the end of the illness. This would result in a lower impact on health-related quality of life, with an overall lower average quality of life decrement, compared with a reduction in symptoms at the beginning of the illness. The Committee noted that the Assessment Group estimated that in such a circumstance the average decrement in quality of life should be reduced to between 0.22 and 0.23 for healthy populations. The Committee considered that people in the 'at risk' population would be expected to have more severe symptoms for a longer period and that it is plausible that having to visit their GP to obtain treatment in the early phase of the illness might in itself cause additional impact on health-related quality of life. Therefore, taking all of these factors into account, the Committee accepted the average base-case decrement in quality of life for 'at risk' populations used in the Assessment Group base case (that is, between 0.5 and 0.6).

4.3.15 The Committee then considered the cost-effectiveness estimates for oseltamivir and zanamivir treatment in otherwise healthy populations. It considered that the most plausible presented ICERs in this group were from the scenarios exploring the combined effect of excluding hospitalisation and mortality benefits, increased GP consultation rates

with a subsequent reduction in the probability that an influenza-like illness is true influenza and a reduced decrement in quality of life of 0.2. The point estimate ICERs resulting from these scenarios ranged from £21,000 to £31,500 per QALY gained in healthy children and from £39,900 to £65,600 per QALY gained for healthy adults. The Committee was also mindful of its conclusion that in children 56% is an overestimate of the probability that influenza-like illness is influenza, and that the estimate should be more closely aligned with that for adults (that is, 41%). Hence it considered that the ICERs of £21,000 to £31,500 per QALY gained in healthy children were underestimates of the true ICERs within the preferred set of assumptions accepted by the Committee. The Committee was also aware that the ICERs presented assumed treatment with oseltamivir in all cases, because oseltamivir dominated zanamivir in healthy populations. The Committee was mindful that if both oseltamivir and zanamivir were recommended, then the true ICERs for healthy populations would be higher. Therefore, the Committee concluded that oseltamivir and zanamivir for the treatment of influenza in otherwise healthy children and adults would not be a cost-effective use of NHS resources.

4.3.16 The Committee further considered the cost-effectiveness estimates of oseltamivir and zanamivir in 'at-risk' populations. Having reviewed a number of the key parameters from the economic models, the Committee concluded that for 'at-risk' populations the economic estimates submitted by the Assessment Group and the manufacturer of oseltamivir were plausible. The Committee concluded that because the base-case estimates were all less than £20,000 per QALY gained for these population subgroups, then oseltamivir and zanamivir, within their licensed indications, could be recommended as cost-effective uses of NHS resources.

4.3.17 The Committee then discussed whether both oseltamivir and zanamivir should be recommended for the treatment of influenza. The Committee was aware of the limitations in the evidence base for comparative efficacy of the two drugs and it was not persuaded that there was evidence of differential effectiveness. However, the Committee noted that the drugs were administered differently and that zanamivir was not licensed for children aged 5 years or younger. The Committee concluded

that it was therefore preferable not to give specific recommendations for oseltamivir or zanamivir, and that the decision as to which to prescribe should be made after consultation between the healthcare professional, the patient and carers on a case-by-case basis, taking into account the patient's preferences regarding drug delivery and potential adverse effects and contraindications. However, the Committee considered that if all other considerations are equal, the choice should be based on the less costly option within the marketing authorisations of the products.

4.3.18 The Committee considered the need for managing outbreaks that occur outside the influenza season as defined by the surveillance threshold. It noted that such outbreaks often occurred in residential care establishments and were frequently associated with poor outcomes and complications in vulnerable populations. The Committee noted that the population in residential care was most likely to be older people or people otherwise at risk of influenza complications. It was mindful that, because oseltamivir and zanamivir are effective only against true influenza, the cost effectiveness of treatment in such situations would depend on the probability that the influenza-like illness was influenza. The Committee noted that this probability was low in the absence of wider circulation of influenza. Therefore, the Committee considered it important that in such situations there should be firmer evidence that the influenza-like illness was influenza. Such evidence could be supplied by virological testing. The Committee considered other people who lived together in a residential setting, such as a prison or boarding school. It noted that such populations would comprise mostly healthy people for whom the consequences of influenza infection would be minor. The Committee agreed that such populations would not be exceptions and treatment during outbreaks outside the influenza season would not be cost effective unless people in those populations were in an 'at-risk' group. Therefore the Committee recommended that outside the periods when national surveillance indicates that influenza virus is circulating, oseltamivir and zanamivir could be recommended for treatment of influenza in 'at-risk' people living in long-term residential or nursing homes, but only if there is a high level of certainty that a localised outbreak is occurring, usually based on virological evidence of infection with influenza in the incident case or cases.

5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2 'Healthcare standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health boards and NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3 NICE has developed tools to help organisations implement this guidance (listed below).

- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 The Committee recommended that a UK observational database is established to monitor the effectiveness of influenza treatment with the antiviral drugs oseltamivir and zanamivir. The Committee also recommended that cases of antiviral resistance to oseltamivir and zanamivir are monitored via the observational database.

6.2 The Committee recommended that further research is conducted into the probability that an influenza-like illness is true influenza.

7 Related NICE guidance

- Respiratory tract infections – antibiotic prescribing. Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. NICE clinical guideline 69 (2008).
- Oseltamivir, amantadine (review) and zanamivir for the prophylaxis of influenza. NICE technology appraisal guidance 158 (2008).

8 Review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be considered for review in November 2013.

Andrew Dillon
Chief Executive
February 2009

Appendix A: Appraisal Committee members, and NICE project team

A Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice-chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam
Radiologist, St George's Hospital, London

Professor AE Ades
Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

Dr Amanda Adler
Consultant Physician, Cambridge University Hospitals Trust

Dr Tom Aslan
General Practitioner, London

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, Leicester Royal Infirmary

Mrs Elizabeth Brain
Lay member

Dr Matt Bradley
Head of HTA and Business Development, Sanofi-aventis UK

Dr Robin Carlisle
Deputy Director of Public Health, Rotherham Primary Care Trust

Dr Karl Claxton
Professor of Health Economics, Department of Economics and Related Research, University of York

Dr Simon Dixon
Reader in Health Economics, University of Sheffield

Mrs Fiona Duncan
Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Dr Paul Ewings
Statistician, Taunton and Somerset NHS Trust, Taunton

Professor John Geddes
Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston
Chief Executive, Barking, Havering and Redbridge Hospitals NHS Trust

Mr Adrian Griffin
VP Strategic Affairs, LifeScan, Johnson and Johnson

Dr Richard Harling
Director of Public Health, Worcestershire Primary Care Trust and Worcestershire County Council.

Professor Philip Home (Vice-Chair)
Professor of Diabetes Medicine, Newcastle University

Dr Terry John
General Practitioner, London

Dr Vincent Kirkbride
Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Dr Simon Maxwell
Senior Lecturer in Clinical Pharmacology and Honorary Consultant Physician, Queen's Medical Research Institute, University of Edinburgh

Dr Alec Miners
Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr Ann Richardson
Lay member

Mrs Angela Schofield
Chairman, Bournemouth and Poole Teaching Primary Care Trust

Mr Mike Spencer
General Manager, Facilities and Clinical Support Services, Cardiff and Vale NHS Trust

Dr William Turner
Consultant Urologist, Addenbrooke's Hospital, Cambridge University Hospitals NHS Trust

Dr Simon Thomas
Consultant Physician and Reader in Therapeutics, Newcastle Hospitals NHS Foundation Trust and Newcastle University

Mr David Thomson
Lay member

Dr Luke Twelves
General Practitioner, Cambridgeshire

Dr Norman Vetter
Reader, Department of Primary Care and Public Health, School of Medicine, University of Cardiff

Dr Paul Watson
Director of Commissioning, East of England Strategic Health Authority

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Rebecca Trowman
Technical Lead

Helen Chung
Technical Adviser

Eloise Saile
Project Manager (until September 2008)

Bijal Chandarana
Project Manager (from September 2008)

Appendix B: Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by the Centre for Reviews and Dissemination, University of York.

- Burch J, Paulden M, Conti S et al. Antiviral drugs for the treatment of influenza: a systematic review and economic evaluation, July 2008.

B. The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I and II were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I) Manufacturers/sponsors:

- Alliance Pharmaceuticals (amantadine)
- GlaxoSmithKline (zanamivir)
- Roche Products (oseltamivir)

II) Professional/specialist and patient/carer groups:

- Diabetes UK
- British Paediatric Respiratory Society
- British Thoracic Society
- Health Protection Agency
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists

- Royal College of Physicians
- Royal Pharmaceutical Society

III) Other consultees

- Cornwall and the Isles of Scilly Primary Care Trust
- Department of Health
- Dudley Primary Care Trust
- Welsh Assembly Government

IV) Commentator organisations (did not provide written evidence and without the right of appeal)

- British National Formulary
- Cancer Care Cymru
- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Welsh Kidney Patients Association
- NHS Centre for Reviews and Dissemination and Centre for Health Economics, York
- National Coordinating Centre for Health Technology Assessment

C. The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on amantadine, oseltamivir and zanamivir for the treatment of influenza (review of existing guidance TA 58) by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Will Carroll, Consultant Paediatrician, nominated by the British Paediatric Respiratory Society Research Committee – clinical specialist

- Dr Wei Shen Lim, Consultant Respiratory Physician, nominated by the Health Protection Agency – clinical specialist
- Dr Maria Zambon, Clinical Expert, nominated by the Health Protection Agency – clinical specialist

Changes after publication

February 2014: minor maintenance

March 2012: minor maintenance

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE multiple technology appraisal process.

It replaces 'Flu treatment – zanamivir (review), amantadine and oseltamivir' (NICE technology appraisal 58).

The review and re-appraisal of amantadine, oseltamivir and zanamivir for the treatment of influenza has resulted in a change in the guidance. Specifically:

- people with chronic neurological conditions and people with chronic liver disease are now considered 'at risk'
- zanamivir is now recommended as a treatment option for children between the ages of 5 and 12 years in 'at-risk' groups if influenza is circulating and they can start treatment within 36 hours of first symptoms
- oseltamivir and zanamivir are now recommended as treatment options for 'at-risk' people in long-term and residential nursing homes during localised outbreaks (when influenza is not circulating), if there is a high level of certainty that the causative agent is influenza.

This guidance has been prepared in the expectation that vaccination against influenza is undertaken in accordance with national guidelines. Vaccination has been established as the first-line intervention to prevent influenza and its complications, and the use of drugs described in this guidance should not in any way detract from efforts to ensure that all eligible people receive vaccination.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration

of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

Accreditation