NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Oseltamivir, amantadine and zanamivir for the prophylaxis of influenza (including a review of NICE technology appraisal guidance 67)

1 Guidance

This guidance has been prepared with 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 as recommended in this guidance should not detract from efforts to ensure that all eligible people receive vaccination.

This guidance does not cover the circumstances of a pandemic, an 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 post-exposure prophylaxis of influenza if all of the following circumstances apply.

- National surveillance schemes have indicated that influenza virus is circulating.
- The person is in an at-risk group as defined in section 1.3.
- The person has been exposed (as defined in section 1.4) to an influenza-like illness and is able to begin prophylaxis within the timescale specified in the marketing authorisations of the individual drugs (within 36 hours of contact with an index case for zanamivir and within 48 hours of contact with an index case for oseltamivir)

- The person has not been effectively protected by vaccination (as defined in section 1.5).

1.2 The choice of either oseltamivir or zanamivir in the circumstances described in section 1.1 should be determined by the healthcare professional in consultation with patients and carers. The decision should take into account preferences regarding the delivery of the drug and potential adverse effects and contraindications. If all other considerations are equal, the drug with the lower acquisition cost should be used.

1.3 For the purpose of this guidance, people at risk are defined as those who fall into one or more of the clinical risk groups defined, and updated, each year by the Chief Medical Officer. The current list includes people with:

- chronic respiratory disease (including asthma that requires continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission)
- chronic heart disease
- chronic renal disease
- chronic liver disease
- chronic neurological disease
- immunosuppression
- diabetes mellitus.

People who are aged 65 years or older are also defined as at-risk for the purpose of this guidance.

1.4 Exposure to an influenza-like illness is defined as close contact with a person in the same household or residential setting who has had recent symptoms of influenza.

1.5 People who are not effectively protected by vaccination include:

- those who have not been vaccinated since the previous influenza season
- those for whom vaccination is contraindicated, or in whom it has yet to take effect
- those who have been vaccinated with a vaccine that is not well matched (according to information from the Health Protection Agency) to the circulating strain of influenza virus.

1.6 During localised outbreaks of influenza-like illness (outside the periods when national surveillance indicates that influenza virus is circulating generally in the community), oseltamivir and zanamivir may be used for post-exposure prophylaxis in at-risk people living in long-term residential or nursing homes, whether or not they are vaccinated. However, this should be done 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 infection with influenza in the index case or cases.

1.7 Oseltamivir and zanamivir are not recommended for seasonal prophylaxis of influenza.

1.8 Amantadine is not recommended for the prophylaxis of influenza.

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 are fever accompanied by respiratory symptoms such as sneezing, coughing, runny nose and sore throat and systemic symptoms such as malaise, myalgia, chills and headaches. Gastrointestinal symptoms such as nausea, vomiting and diarrhoea are also common. 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.

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 is commonly transmitted through household contacts, with the highest attack rates in children. People who live in residential accommodation and those who work in healthcare settings are at a higher risk of infection. The influenza attack rate is the probability that a person develops influenza over the influenza season. It is expressed as the proportion of people exposed to risk who develop the disease during the period under consideration. The influenza attack rate depends on the circulating level of influenza. It is estimated that yearly influenza epidemics in the UK cause between 12,000 and 13,800 deaths.

2.3 Influenza-like illness, which can be caused by a variety of infectious agents, is a clinical diagnosis made on the basis of symptoms. The causative agent for an influenza-like illness cannot be determined clinically and diagnosis requires laboratory testing. 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 England, normal seasonal activity is currently 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 oseltamivir and amantadine for the prophylaxis of influenza’ (NICE technology appraisal guidance 67).

Accurate monitoring of influenza activity requires analysis of clinical, virological and epidemiological information.

2.4 The management of influenza is supportive and consists of relieving symptoms while awaiting recovery. For people in at-risk groups who can start therapy within 48 hours of the onset of an influenza-like illness, treatment with the antiviral drugs oseltamivir or zanamivir is recommended in line with 'Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza' (NICE technology appraisal guidance 58). Complications require specific management, and antibiotics are used for secondary bacterial infections.

2.5 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. Such people are those with chronic respiratory, cardiovascular, 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.

2.6 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). If seasonal prophylaxis is given, it is carried out 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.

3 The technologies

Oseltamivir

3.1 Oseltamivir (Tamiflu, Roche) 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 marketing authorisation for post-exposure prophylaxis in people 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community. The appropriate use of oseltamivir for prevention of influenza should be determined on a case-by-case basis by the circumstances and the population requiring protection. In exceptional situations (for example in the case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention can be considered in people 1 year of age or older. For post-exposure prophylaxis, oseltamivir should be started within 48 hours of contact with an index case of influenza-like illness and continued for 10 days. For seasonal prophylaxis, oseltamivir is given for up to 6 weeks. Oseltamivir is administered orally.

3.2 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, hepatobiliary system disorders have been reported. Convulsions and psychiatric events, 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 summary of product characteristics (SPC).

3.3 Oseltamivir costs £16.36 for a 10-day course for an adult (excluding VAT; 'British national formulary' [BNF] edition 54). Costs may vary in different settings because of negotiated procurement discounts.

Amantadine

3.4 Amantadine (Lysovir, Symmetrel, Alliance Pharmaceuticals) acts against influenza A virus by blocking viral replication. The marketing authorisation recommends amantadine prophylactically in people particularly at risk. This can include those with chronic respiratory disease or debilitating conditions, the elderly and those living in crowded conditions. It can also be used for members of families in which influenza has already been diagnosed, for control of institutional outbreaks or for those in essential services who are unvaccinated or when vaccination is unavailable or contraindicated. It is also recommended as post-exposure prophylaxis in conjunction with inactivated vaccine during an outbreak until protective antibodies develop, or in people who are not expected to have a substantial antibody response (because of immunosuppression). Amantadine is licensed for use in people aged 10 years or older. The SPC states that treatment is recommended for as long as protection from infection is required and that in most instances this is expected to be for 6 weeks. In clinical practice this corresponds to its use as seasonal prophylaxis. For post-exposure prophylaxis, amantadine is usually given for 4–5 days. Amantadine is administered orally.

3.5 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.

3.6 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; BNF edition 54). 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 marketing authorisation for post-exposure prophylaxis of influenza A and B in adults and children (5 years and older) following contact with a clinically diagnosed case in a household. In exceptional circumstances, zanamivir may be considered for seasonal prophylaxis of influenza A and B (for example, during a community outbreak in the case of a mismatch between circulating and vaccine strains, and in a pandemic situation). For post-exposure prophylaxis zanamivir should be initiated within 36 hours of contact with an index case of influenza-like illness and continued for 10 days. For seasonal prophylaxis, zanamivir is given for up to 28 days. Zanamivir is administered by oral inhalation using an inhaler 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 to £16.36 for a 10-day course. The price of zanamivir currently listed in the BNF is £24.55 for a 10-day course (excluding VAT; BNF edition 54). 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 carried out a systematic search for randomised controlled trials (RCTs) conducted in people in contact with clinically diagnosed influenza or people for whom seasonal prophylaxis would be appropriate. The population was divided into children, adults and older people, with each group being further subdivided into healthy or at risk of developing complications of influenza. The three drugs could be used for seasonal or post-exposure prophylaxis, with outbreak control referring to post-exposure prophylaxis in settings where people live or work in close proximity (for example, in residential care). Twenty-two RCTs were identified by the systematic review and a further RCT was provided in a sponsor's submission. No head-to-head RCTs were identified. The background circulating levels of influenza for the duration of the individual RCTs were often not reported clearly.

4.1.2 In most RCTs, the effectiveness of antiviral drugs was measured as cases of influenza prevented. Cases of influenza were defined as either symptomatic laboratory-confirmed influenza or clinical illness. The efficacy outcome was presented as the relative risk and protective (or prophylactic or preventive) efficacy of developing influenza with and without prophylaxis. The relative risk is the ratio of the proportion of people developing influenza in the treatment group to the proportion developing influenza in the control group. The lower the relative risk the higher the efficacy of prophylaxis. The protective efficacy is the percentage of people for whom prophylaxis could prevent infection. It is calculated by subtracting the relative risk from 1 (and is expressed as a percentage).

4.1.3 Evidence was submitted by consultees that the incidence of influenza-like illness has been falling consistently over the last 10 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 and virus isolation from clinical specimens. Lastly, it was apparent that outbreaks of influenza occur within localised areas, especially in residential care settings, outside of the influenza season.

Oseltamivir

4.1.4 Two RCTs of oseltamivir for seasonal prophylaxis, both included in the previous appraisal (TA67), were in healthy adults and one was in older people within a residential care setting. A meta-analysis of the two seasonal prophylaxis trials in adults (n = 1039) gave a relative risk of developing symptomatic laboratory-confirmed influenza of 0.27 (95% confidence interval [CI] 0.09 to 0.83). The study (n = 548) of seasonal prophylaxis in older people showed a 92% protective efficacy for symptomatic laboratory-confirmed influenza (p = 0.002), with an 86% relative reduction in secondary complications.

4.1.5 Two studies, one of which was not included in the original appraisal, were of post-exposure prophylaxis in households with mixed populations of adults and children. These two RCTs (n = 1747) showed a protective efficacy against symptomatic laboratory-confirmed influenza of 89% (p < 0.001) in one study and 73% in the other. When the results of the two RCTs were pooled by meta-analysis, the resulting relative risk was 0.19 (95% CI 0.08 to 0.45) and the protective efficacy was therefore 81%. Analysis of data limited to children aged 1–12 years from another trial of post-exposure prophylaxis showed a protective efficacy of 64% (relative risk 0.36).

4.1.6 The Assessment Group stated that oseltamivir was of equivalent efficacy in vaccinated and unvaccinated people. No evidence of reduced sensitivity was observed in trials but surveillance data suggest viral resistance to oseltamivir is emerging.

Amantadine

4.1.7 No new RCTs of amantadine additional to those considered in the previous appraisal (TA67) were identified. Of three trials of seasonal prophylaxis two trials were in unvaccinated healthy adults and one trial in older people in residential care who were inadequately vaccinated. In one study in healthy adults (n = 318), the relative risk for clinical symptoms with amantadine prophylaxis was 0.4 (95% CI 0.08 to 2.03). Another study (n = 285) in healthy military personnel found no difference in the incidence of acute respiratory illness. The studies of the efficacy of seasonal prophylaxis were limited by low attack rates. For the trial in older people in residential care no results were reported as there was no evidence of an influenza epidemic in this group during the trial.

4.1.8 Two trials investigated outbreak control, one in healthy mostly vaccinated adolescents and one in healthy unvaccinated adults. The study (n = 536) of outbreak control in vaccinated adolescent males in a boarding school reported a relative risk of 0.17 (95% CI 0.08 to 0.37) for clinical influenza and a protective efficacy of 90% (95% CI 0.66 to 0.97) for symptomatic laboratory-confirmed influenza. This study also demonstrated that the protective effect of amantadine prophylaxis was limited to the period of prophylaxis. The second study (n = 10,053) of outbreak control in unvaccinated adults in semi-isolated engineering schools reported a relative risk for clinical influenza of 0.59 (95% CI 0.49 to 0.70) with amantadine prophylaxis and showed some evidence that prophylaxis reduced the severity and duration of influenza illness.

4.1.9 The Assessment Group could not draw firm conclusions about the impact of vaccination status on the efficacy of amantadine prophylaxis. No information was available from the RCTs on the degree of viral resistance. However, virological monitoring has documented resistance to amantadine and it is reported that 37% of viral isolates are resistant to amantadine. Development of resistance can occur relatively rapidly during treatment and can lead to the failure of prophylaxis.

Zanamivir

4.1.10 Four new trials not included in the previous appraisal (TA67) were identified by the Assessment Group: one of seasonal prophylaxis in at-risk adolescents and adults, one of post-exposure prophylaxis in a mixed population, and two of outbreak control in at-risk older people in residential care. A further new RCT, of seasonal prophylaxis in healthcare workers, formed part of the sponsor submission. A trial (n = 1107) of zanamivir as seasonal prophylaxis in healthy adults showed a protective efficacy of 68% (95% CI 37 to 83) against symptomatic laboratory-confirmed influenza. The trial was conducted in an influenza season where the vaccine and circulating strain were mismatched. In the unvaccinated subgroup, the protective efficacy was 60% (95% CI 24 to 80). A second study (n = 319) of zanamivir for seasonal prophylaxis in healthcare workers showed no statistically significant difference in the development of symptomatic laboratory-confirmed influenza. There was also a study (n = 3363) of zanamivir for seasonal prophylaxis in community-dwelling at-risk adolescents and adults (aged 12 years and above). For the intent-to-treat population the protective efficacy against symptomatic laboratory-confirmed influenza was 83% and the relative risk was 0.17 (95% CI 0.07 to 0.44). The relative risk did not vary according to vaccination status. The relative risk for developing confirmed influenza with complications was 0.12 (95% CI 0.02 to 0.73). The subgroup of

people aged 65 and above, some of whom had further risk factors for influenza complications, showed a relative risk of 0.20 (95% CI 0.02 to 1.72).

4.1.11 A trial (n = 1291) of zanamivir given for 10 days for post-exposure prophylaxis to all household contacts (aged 5 years or older) of a person with an influenza-like illness showed a relative risk for symptomatic laboratory-confirmed influenza of 0.18 (95% CI 0.08 to 0.39). Another trial (n = 837) of 10-day zanamivir for post-exposure prophylaxis in household contacts showed a protective efficacy of 79% (95% CI 62 to 89, relative risk 0.21). Fewer households in the treatment group had contacts who developed complications of laboratory-confirmed influenza (p = 0.01). Two trials (reported jointly; n = 288) investigated the use of zanamivir for 5 days for post-exposure prophylaxis in household contacts. The relative risk for developing symptomatic laboratory-confirmed influenza was 0.33 during prophylaxis, and the length of illness was shorter in the treatment group (p = 0.016).

4.1.12 Two studies (n = 519) investigated the prevention of influenza outbreaks in older people in long-term residential care. The available data from one of these trials are limited. The second trial was conducted in mostly unvaccinated people and prophylaxis conferred a protective efficacy for symptomatic laboratory-confirmed influenza of 32% during influenza A outbreaks (95% CI 27 to 67).

4.1.13 Some studies tested the susceptibility of viral isolates to zanamivir and found no evidence of viral resistance.

4.2 Cost effectiveness

4.2.1 The Assessment Group identified seven cost-effectiveness studies that included oseltamivir, amantadine or zanamivir for the prophylaxis of influenza, one of which was a sponsor submission

from the manufacturer of oseltamivir. No cost-effectiveness analyses were submitted by the manufacturers of amantadine and zanamivir. Three cost-effectiveness studies were UK based and took an NHS perspective (including the assessment for the original appraisal, TA67). One study from the UK NHS perspective estimated that the cost effectiveness of oseltamivir for post-exposure prophylaxis compared with no prophylaxis or treatment was approximately £30,000 per quality-adjusted life year (QALY) gained and compared with no prophylaxis followed by oseltamivir treatment was about £52,000 per QALY gained. The second UK study, the assessment undertaken for the original appraisal, included vaccination as a prophylactic strategy. The model related to seasonal prophylaxis only. All three drug strategies were dominated by vaccination as a prophylactic strategy.

4.2.2 The submission from the manufacturer of oseltamivir reported a model to estimate the cost effectiveness of oseltamivir for seasonal and post-exposure prophylaxis of influenza, comparing it with amantadine, zanamivir and no prophylaxis for adults and children older than 12 years who were healthy or at risk, and for children aged 1–12 years and 1–5 years. A cost-effectiveness analysis was undertaken for the comparison of oseltamivir with amantadine or usual care. For the comparison of oseltamivir with zanamivir, it was assumed that both drugs are equally effective and a cost-minimisation analysis was undertaken. The Assessment Group reanalysed the results from the manufacturer's model for oseltamivir to generate full incremental cost-effectiveness estimates (the manufacturer's submission presented pair-wise comparisons rather than a full incremental analysis). Oseltamivir for post-exposure prophylaxis gave incremental cost-effectiveness ratios (ICERs) below £8000 per QALY gained for both groups of children, less than £2000 for at-risk adults and about £27,000 for healthy adults. For children in both age groups oseltamivir as

seasonal prophylaxis gave ICERs above £46,000 per QALY gained. For healthy or at-risk adults and children (older than 12 years) oseltamivir was dominated by zanamivir (it was less effective and more costly), and for the at-risk group the ICERs for amantadine and zanamivir were less than £16,000 per QALY gained. The model was sensitive to the changes in assumptions for attack rates and the number of GP visits per household.

4.2.3 The Assessment Group conducted an independent economic assessment. The three drugs were compared with each other and with no prophylaxis for three age groups: 'children' (aged 1–14 years), 'adults' (aged 15–64 years) and 'older people' (older than 65 years). Each age group was subdivided into healthy and at risk, and each of these six subgroups was further divided on the basis of vaccination status.

4.2.4 The model assumed that prophylaxis would only be considered when it is known that influenza is circulating in the community above a threshold of 30 new GP consultations for influenza-like illness per week per 100,000 population. The duration of the influenza season was calculated as the period for which the number of new GP consultations for influenza-like illness per week was above the threshold level of 30 (previously 50) per 100,000 population for the past 20 influenza seasons (1987–88 to 2006–07).The mean duration of the influenza season was calculated to be 5.71 weeks. It was assumed that vaccination is effective over the whole of the season but that drugs are effective only during the period over which they are taken. Hence the preventive efficacy of antivirals was adjusted according to the proportion of the influenza season for which the drugs were taken.

4.2.5 The model did not consider the benefits of prophylaxis in preventing transmission of influenza from the person who receives

prophylaxis to others who might otherwise have contracted the illness from this person.

4.2.6 The probability that a person exposed to the influenza virus develops influenza depends on the influenza attack rate, the prophylactic efficacy of the intervention strategy and the person's vaccination status. For amantadine it also depends on the probability that influenza is of type A, and on the degree of resistance of the virus to the drug. The baseline influenza attack rate is the probability that a person develops influenza over the influenza season. The model assumed this differs in each age group and within the models for seasonal and post-exposure prophylaxis. For seasonal prophylaxis the probability was 0.174 in children, 0.062 in adults and 0.052 in older people. For post-exposure prophylaxis it was 0.189 in children, 0.088 in adults and 0.088 in older people. The probability that influenza-like illness was true influenza was derived from Royal College of General Practitioners' data. This was estimated to be 0.5 across all groups. The probability that influenza was influenza A virus was based on virological surveillance data for 12 influenza seasons (1995–96 to 2006–07). The overall mean probability that a case of influenza was influenza A was estimated to be 0.72.

4.2.7 The protective efficacies of vaccination, amantadine, oseltamivir and zanamivir were derived from the review of clinical effectiveness (and Cochrane reviews for vaccination). The relative risks for vaccination were 0.36 for healthy children, 0.35 for healthy adults and 0.42 for older people. The protective efficacy of vaccination reduced the probability of developing influenza without prophylaxis in the model. The joint benefit of vaccination and prophylaxis was assumed to be cumulative – that is, the effectiveness of prophylaxis was applied only to the unvaccinated proportion of the population.

4.2.8 There was a lack of clinical-effectiveness evidence for a number of subgroups in the cost-effectiveness analysis. Because of this lack of evidence the relative risk for seasonal prophylaxis with amantadine was taken from a study of unvaccinated healthy adults and applied to all population subgroups. For post-exposure prophylaxis with amantadine, efficacy was taken from a single study of outbreak control in vaccinated healthy adolescents and applied to all groups in the model. The model also assumed, based on data from the 2006–07 season, that in 37% of influenza cases people were resistant to amantadine. For seasonal prophylaxis with oseltamivir the results of the study in healthy unvaccinated adults were applied to healthy and at-risk adults and children, and the results of the trial in at-risk people in residential care were applied to healthy and at-risk older people. For post-exposure prophylaxis with oseltamivir, a meta-analysis was performed of two trials from healthy adults. The results were applied to the healthy and at-risk adult and older subgroups, and the results of the subgroup analysis for children in these trials were applied to the healthy and at-risk child subgroups. For zanamivir seasonal prophylaxis, a trial in healthy and mostly unvaccinated adults was used to calculate the relative risk for the healthy adults and the child groups (both at risk and healthy). A study of seasonal prophylaxis in at-risk adults supplied estimates for the at-risk adult and the older populations. For post-exposure prophylaxis with zanamivir a meta-analysis of three trials in adults and children was conducted and the results applied to all population groups.

4.2.9 The model included the probability of adverse effects from vaccination and amantadine only. Adverse effects from oseltamivir and zanamivir were assumed to be mild and self-limiting and not to have an impact on a person's health-related quality of life.

4.2.10 The model also included the probabilities of developing complications from influenza or influenza-like illness, of receiving

antibiotics, of hospitalisation because of a complication (including intensive care treatment), and of death from a complication related to an influenza-like illness.

4.2.11 Estimates of health-related quality of life were obtained from oseltamivir studies. The method for obtaining utility values used in the model was non-reference case, derived from measures on a 10-point scale from the oseltamivir trials. The adverse effects of amantadine were assumed to cause a 0.2 utility decrement for a mean duration of 5 days. Health utility decrements associated with complications of influenza-like illness were derived from a study that used committee consensus to reach estimates and were assumed to operate for the duration of complications in clinical trials for oseltamivir.

4.2.12 The model included costs for acquisition and administration of vaccination and antiviral prophylaxis and treatment, costs associated with the management of adverse effects, consultation costs, and the costs of antibiotics and hospitalisation, including intensive care. In the base case, the model assumed that each prescription of prophylaxis required a separate GP consultation.

4.2.13 Sensitivity analyses were carried out using the new lower price for zanamivir which changed during the course of the appraisal. The effect of multiple prescriptions per GP consultation (for example, for family contacts) was explored. Seasonal prophylaxis would be considered in the exceptional event of a mismatch between circulating and vaccine virus strains. In such a situation the protective efficacy of vaccination would decrease, the extent of such a decrease being determined by the degree of mismatch. This was explored by analyses in which the relative risk for vaccination was 0.5 or 0.75. Because the trials for oseltamivir and zanamivir occurred in different settings with differing circulating levels of influenza, virus strains and populations, the differing estimates of

efficacy are not strictly comparable. To explore the impact of this, an analysis was conducted in which both drugs were considered to be of equal efficacy. Further analyses exploring the effect of assuming resistance to oseltamivir and varying the influenza attack rates were also conducted.

4.2.14 The Assessment Group model gave the following results for seasonal prophylaxis. In healthy children, oseltamivir economically dominated amantadine and zanamivir. That is, treatment with oseltamivir was expected to cost less and result in more QALYs gained. For unvaccinated children the ICER was £44,007 per QALY gained and for vaccinated children it was £129,357 per QALY gained. For at-risk children oseltamivir dominated the other drugs, with an ICER of £16,630 per QALY gained for unvaccinated children and £51,069 per QALY gained for vaccinated children. In healthy adults oseltamivir dominated the other drugs, with ICERs of £147,505 per QALY gained in unvaccinated adults and £427,184 per QALY gained in vaccinated adults. For at-risk adults oseltamivir again dominated the other drugs, with ICERs of £63,552 per QALY gained in unvaccinated people and £186,651 per QALY gained in vaccinated people. For healthy older people oseltamivir dominated the other drugs, with ICERs of £49,742 per QALY gained in unvaccinated people and £121,728 per QALY gained in vaccinated people. In at-risk older people oseltamivir dominated the other drugs, with ICERs of £38,098 per QALY gained for unvaccinated people and £93,763 per QALY gained for vaccinated people.

4.2.15 For post-exposure prophylaxis in healthy children zanamivir economically dominated oseltamivir and amantadine, with ICERs of £23,225 per QALY gained in unvaccinated children and £71,648 per QALY gained in vaccinated children. For post-exposure prophylaxis in at-risk children zanamivir dominated the other drugs, with ICERs of £8233 for unvaccinated children and £27,684 for vaccinated children. For post-exposure prophylaxis in healthy

adults oseltamivir dominated zanamivir and amantadine, with ICERs of £34,181 for unvaccinated adults and £103,706 for vaccinated adults. For post-exposure prophylaxis in at-risk adults oseltamivir dominated the other drugs, with ICERs of £13,459 per QALY gained for unvaccinated adults and £43,970 for vaccinated adults. In healthy older people oseltamivir dominated zanamivir and amantadine, with an ICER of £10,716 per QALY gained for unvaccinated people and £28,473 for vaccinated people. For post-exposure prophylaxis in at-risk older people oseltamivir again dominated, with ICERs of £7866 for unvaccinated people and £21,608 for vaccinated people.

4.2.16 When the lower price of zanamivir was used in the economic model it had little impact on the outcome of the comparisons made in the base case for seasonal prophylaxis except for at-risk adults. In this group zanamivir was no longer dominated by oseltamivir; the ICER was £53,159 per QALY gained for zanamivir compared to no treatment. For post-exposure prophylaxis the price reduction led to improvements in the cost effectiveness of zanamivir for healthy and at-risk children. In general, the estimates for cost effectiveness were sensitive to the influenza attack rates, the level of viral resistance, vaccine efficacy, the threshold used to define when influenza is circulating in the community, the relative efficacy of oseltamivir and zanamivir and the risk of hospitalisation in people without complications. For seasonal prophylaxis, the estimates were sensitive to the discount rate and for post-exposure prophylaxis they were sensitive to the use of multiple prescriptions for prophylaxis per GP visit.

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of oseltamivir, amantadine and zanamivir, having considered evidence on the nature of the

condition and the value placed on the benefits of oseltamivir, amantadine and zanamivir by people with exposure to influenza-like illness, 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 accepted 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 prophylaxis 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 appropriately been established as the first-line intervention to prevent influenza and its complications, and was mindful that the use of drug prophylaxis should not in any way detract from efforts to ensure that all eligible people are vaccinated at the beginning of each influenza season. However, the Committee also accepted that because of the antigenic variation in circulating influenza viruses, vaccination may not always be fully effective in a particular season and thus a mismatch between vaccine and circulating virus strains could result in vaccination conferring significantly lower protection than predicted.

4.3.3 Because prophylaxis is given after contact with a person with clinically defined influenza-like illness and not confirmed influenza, the Committee accepted that a crucial factor in determining the effectiveness and cost effectiveness of antiviral drugs would be the probability that a person with influenza-like illness has true influenza. The Committee agreed that this probability would be highest when the virus was known to be circulating in the community, and that a method of routinely identifying periods of circulation of influenza viruses was needed in order to determine

when influenza prophylaxis should be recommended. Such a method would need to take account both of the probability that influenza-like illness was influenza and of the influenza attack rate because the cost effectiveness depended on the assumptions for both these parameters.

4.3.4 The Committee noted that the surveillance scheme used to determine levels of influenza activity in the community (as recommended by the Health Protection Agency) 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 heard from clinical specialists that the threshold levels were an artificial construct that may not be suitable for defining when drug prophylaxis would be most efficacious because they were not created for this purpose.

4.3.5 The Committee was aware that virological testing was possible and that results could be available within 24–48 hours. However, the Committee recognised that routine testing in individual cases was impractical and that the delay caused by awaiting test results could affect the timing of the use of prophylaxis with respect to the exposure to infection and therefore alter its efficacy. The Committee accepted that there were other indicators of influenza activity, both single and in combination, but that the evidence for cost effectiveness placed before it was based on the surveillance scheme threshold levels. The Committee was also aware that outbreaks of influenza were common in localised environments (such as residential care establishments) outside the influenza season as defined by the thresholds, and that unless such outbreaks could also be identified, it would not be possible to establish situations in which the use of prophylaxis would be cost effective.

4.3.6 The Committee considered the evidence for effectiveness of the individual drugs and the emergence of additional evidence since the publication of TA67. The Committee accepted that the submitted evidence indicated that oseltamivir and zanamivir were clinically effective when used either as seasonal or as post-exposure prophylaxis. However there was more limited evidence for the efficacy of amantadine prophylaxis in differing settings. It noted that there were no head-to-head trials of the interventions and that because the individual trials were conducted in differing populations, the results might not reflect accurately any differences in efficacy between the drugs. In addition, the Committee noted that the relative risks used in the economic modelling needed to be extrapolated from existing trials to the many groups for which there is no trial data. Therefore, the Committee noted that it would need to be cautious in appraising the results of the economic analysis for groups for which the suggestion of underlying differences in efficacy between the drugs was based on assumptions and not trial evidence.

4.3.7 The Committee accepted that the neuraminidase inhibitors were generally safe and well tolerated. It was aware of concerns that have been raised with regulatory authorities in Canada, Japan and the USA about possible neuropsychiatric events associated with oseltamivir in adolescents, but that no specific guidance regarding safety has been issued by the European Medicines Agency or the Medicines and Healthcare products Regulatory Agency. The Committee accepted that amantadine was associated with more frequent adverse effects. The Committee also accepted evidence of viral resistance to amantadine, and noted that there was also evidence of increasing resistance to the neuraminidase inhibitors although it was currently low.

4.3.8 The Committee considered the consequences of developing influenza and the costs and health outcomes of these assumed in

the economic model. It was aware of clinical specialist opinion that there was no evidence that the use of prophylaxis decreased hospitalisations associated with influenza-like illness as included in the model. However, the Committee accepted that preventing an influenza infection could logically and plausibly be expected to result in a decrease in the adverse consequences of the illness. The Committee considered the multiple prescriptions by GPs to contacts of a case of influenza-like illness. It was aware that the use of multiple prescriptions could improve the cost effectiveness of prophylaxis. However the Committee was persuaded that prescribing without seeing the patient would not have a straightforward effect on cost effectiveness as additional GP time would be required to ensure safe prescribing and indirect usage may not result in satisfactory adherence. In addition, the Committee considered that this approach would not normally be thought of as good practice and would not be used routinely.

4.3.9 The Committee next considered the structure and general approach of the economic analyses. 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 prophylaxis in preventing general transmission of infection, the development of herd immunity, the potential for the development of drug resistance with wider use of prophylaxis 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 on the other hand there were potential disbenefits that would make prophylaxis less cost effective. The Committee considered that any additional dynamic benefits of drug prophylaxis in a population with an effective vaccination programme in place would be limited. The Committee was also aware that dynamic models were technically

complicated and that the current evidence available to them 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.

4.3.10 The Committee considered the cost effectiveness of the use of seasonal prophylaxis. In doing so it was aware that clinical specialist opinion did not favour the use of drug prophylaxis in this manner. The Committee also noted that because seasonal prophylaxis would be considered only in exceptional situations such as a mismatch between vaccine and circulating virus, the efficacy of vaccination assumed should be intermediate between the extremes of the values used for unvaccinated and vaccinated relative risks in the model. The Committee concluded that the ICERs for the various subgroups examined in the modelling suggested that overall seasonal prophylaxis was not a cost-effective use of NHS resources. The Committee specifically noted that the Assessment Group-modelled ICER for seasonal prophylaxis in unvaccinated at-risk children was approximately £17,000 per QALY gained with a high probability of this being cost effective at a threshold of £20,000. However, this ICER was very sensitive to changes in the assumed attack rate and the Committee was aware that the values for attack rates used in the economic analysis, which were derived from intensively monitored clinical trials, were likely to be higher than those that would be expected to occur routinely in the general population. In addition, the relative risk of infection for this subgroup of children had been extrapolated from a trial in healthy adults and was not based on direct empirical evidence. Therefore the Committee agreed that it could not recommend seasonal prophylaxis with oseltamivir, amantadine or zanamivir.

4.3.11 The Committee considered the results of the economic evaluation for the use of the drugs for post-exposure prophylaxis. The Committee was aware that prophylaxis would not normally be considered in clinical practice for healthy people given the self-limiting nature of influenza and the potential for adverse effects with medication. The Committee noted that the ICERs for the various subgroups indicated that the use of post-exposure prophylaxis was cost effective in at-risk groups only who had either not been vaccinated or not been effectively protected by vaccination. This would include people in whom vaccination was contraindicated or had yet to take effect and circumstances when the vaccine and circulating strains of virus were sufficiently different to mean that vaccination did not provide adequate protection. The ICERs in these subgroups ranged from £7866 per QALY gained for unvaccinated at-risk older people, to £8233 per QALY gained for unvaccinated at-risk children, to £13,459 per QALY gained for unvaccinated at-risk adults. The Committee also noted that the contact with the index case would need to be of a sufficiently intense degree, such as that experienced by living together in the same residential setting, normally the same household. The Committee concluded that post-exposure prophylaxis was a cost-effective use of resources for at-risk persons who were not adequately protected by vaccination, but only when it has been established that influenza is circulating in the community.

4.3.12 The Committee then discussed which, if any, of the two neuraminidase inhibitors should be prescribed if post-exposure prophylaxis was considered appropriate in the subgroups identified. 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 between the two drugs. However, the Committee noted that the drugs were administered differently and that zanamivir was not licensed for

children under 5. The Committee concluded that it was not possible to give specific recommendations for one or other of the neuraminidase inhibitors, and therefore the decision as to which to prescribe should be determined by the healthcare professional in consultation with patients and carers on a case-by-case basis, taking into account preferences regarding the delivery of the drug and potential adverse effects and contraindications. If all other considerations are equal, the choice should be based on the less costly option within the marketing authorisations of the products.

4.3.13 The Committee carefully 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 the neuraminidase inhibitors are only effective against true influenza, the cost effectiveness of the use of prophylaxis 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. In addition, the Committee was aware that in the event of an influenza outbreak within a residential setting, the attack rates were likely to be substantially higher than those used in the base case in the model for post-exposure prophylaxis, and mortality in at-risk subgroups would be significant. In the residential care setting this would therefore result in better cost effectiveness of post-exposure prophylaxis than the model estimates. For the exceptional

circumstances of at-risk people in residential care with a confirmed out-of-season outbreak of influenza the Committee accepted that post exposure prophylaxis with oseltamivir and zanamivir would be a cost effective use of NHS resources. 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 prophylaxis 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 may still used as options for post-exposure prophylaxis in vaccinated or unvaccinated 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.

4.3.14 The Committee noted that there was no new evidence for the efficacy of amantadine in various subgroups since the publication of TA67. In addition, a high incidence of viral resistance to amantadine has developed and, compared with the neuraminidase inhibitors, amantadine is associated with a greater incidence of adverse effects. The Committee noted that the economic analysis did not indicate that amantadine would be a cost-effective use of resources in any subgroup for any indication. Therefore the Committee did not recommend amantadine for prophylaxis of influenza.

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). These are available on our website (www.nice.org.uk/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives which support this locally.

- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 Research is required into methods of delivering zanamivir to the under-5 age group and to establish the effectiveness of such treatment.

6.2 Research is required to develop options for prophylaxis of influenza in infants (under 12 months of age).

7 Related NICE guidance

Published

- Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza. NICE technology appraisal guidance 58 (2003). Available from www.nice.org.uk/TA058. Currently being reviewed.

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 2011. The guidance can be routinely reviewed in 3 years because no changes in the evidence are expected before then.

David Barnett
Chair, Appraisal Committee
July 2008

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.

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, Stockwell, London

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Mrs Elizabeth Brain

Lay member

Professor Karl Claxton

Health Economist, University of York

Simon Dixon

Reader in Health Economics, University of Sheffield

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Mr John Goulston

Director of Finance, Barts and the London NHS Trust

Mr Adrian Griffin

Health Outcomes Manager, Johnson & Johnson Medical

Professor Philip Home (Vice Chair)

Professor of Diabetes Medicine, Newcastle University

Dr Vincent Kirkbride

Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Dr Simon Maxwell

Senior Lecturer in Clinical Pharmacology and Honorary Consultant Physician, Queens 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 PCT

Mr Mike Spencer

General Manager, Facilities and Clinical Support Services, Cardiff and Vale 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 Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

C 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.

Elangovan Gajraj

Technical Lead

Helen Chung

Technical Adviser

Eloise Saile

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by the School of Health and Related Research (ScHARR), University of Sheffield.

- Tappenden, P et al. Oseltamivir, amantadine and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67), February 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 Manufacturer/sponsor:

- Alliance Pharmaceuticals
- GlaxoSmithKline
- Roche Products

II Professional/specialist and patient/carer groups:

- Diabetes UK
- British Thoracic Society
- General Practice Airways Group (GPIAG)
- Health Protection Agency
- 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

- Department of Health
- Monmouthshire LHB
- Newham PCT
- Welsh Assembly Government

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- National Public Health Service for Wales
- NHS Quality Improvement Scotland
- Alliance Pharmaceuticals
- GlaxoSmithKline
- Roche Products
- National Coordinating Centre for Health Technology Assessment
- ScHARR

C The following people 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 Oseltamivir, amantadine and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67) by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Douglas Fleming, Unit Director, The Birmingham Research Unit, Royal College of General Practitioners, nominated by Royal College of General Practitioners – clinical specialist.
- Dr John Watson, Consultant Epidemiologist, Head of the Respiratory Diseases Department, Health Protection Agency, nominated by nominated by Health Protection Agency – clinical specialist.
- Mr Kail Gunaratnam, nominated by Diabetes UK – patient expert.