NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Oseltamivir, amantadine and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67).

Draft scope

Remit/appraisal objective

To review the Institute's earlier advice on the clinical and cost-effectiveness of amantadine and oseltamivir[1], and to advise on the clinical and cost-effectiveness of zanamivir, in their licensed indications for the prevention of influenza A and B, both relative to one another and to best symptomatic care.

Background

Influenza is an acute respiratory illness caused by infection with influenza A and B viruses. Certain groups of people are more at a risk of severe illness, complications and hospitalisation associated with influenza. These include the elderly, infants and people with other chronic illnesses. People living or working in residential care establishments are at greater risk of infection. People at risk include those who

- have chronic respiratory disease
- have significant cardiovascular disease (excluding hypertension only)
- have chronic renal disease
- are immunocompromised
- have diabetes mellitus
- are aged 65 years or older.

Influenza occurs mainly in the winter months and affects all age groups. It causes significant morbidity and increased mortality. The average number of deaths attributed directly to influenza in the UK in non-epidemic years is about 600. The number of deaths that are indirectly attributable to influenza is estimated to be ten times as high. The direct and indirect death rates in epidemic years are higher.

The treatment of influenza is mainly supportive consisting of alleviation of the symptoms and managing any complications that may arise. In at-risk people oseltamivir and zanamivir are recommended for the treatment of an influenza-like illness (ILI) and must be started as soon as possible (and within 48 hours) of the onset of symptoms.

Vaccination is currently the mainstay of influenza prophylaxis and is recommended for the at-risk population prior to each influenza season. The

[1] Guidance on the use of oseltamivir and amantadine for the prophylaxis of influenza. Technology Appraisal 67, September 2003.

anti-viral drugs can also be used prophylactically. Prophylaxis may be seasonal, post-exposure or for outbreak control in residential care. Currently NICE recommends oseltamivir for the prophylaxis of at-risk people who have been in contact with a person with influenza-like symptoms and who are not adequately protected by vaccination and for at-risk people within residential care establishments, following contact, regardless of vaccination status.

People who have influenza-like symptoms may not be suffering from true influenza, as a similar symptom complex can occur in association with a variety of other viral infections. Diagnostic tests for influenza are available but diagnosis is usually made principally on clinical grounds (symptoms and physical signs).

It is recommended that the use of antivirals for the treatment and prevention of influenza should take into consideration official recommendations, the variability of epidemiology, including seasonal variations, epidemics and pandemics and the impact of the disease in different geographical areas and patient populations.

The technologies

Amantadine (Symmetrel, Lysovir, Alliance Pharmaceuticals) holds a marketing authorisation for the prophylaxis and treatment of signs and symptoms of infection caused by influenza A virus. Amantadine specifically inhibits the replication of the influenza A virus by blocking the proton pump of the M_2 protein in the virus. Amantadine is available as syrup and capsules.

Oseltamivir (Tamiflu, Roche) holds a marketing authorisation for the post exposure prevention in adults and children one year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community. In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in adults and children one year of age or older. Oseltamivir is a selective inhibitor of neuraminidase enzymes, which are glycoproteins found on the virion surface. It is active against influenza A and B. It is available as syrup and capsules.

Zanamivir (Relenza, GlaxoSmithKline) holds a marketing authorisation for the post-exposure prophylaxis of influenza A and B in adults and children (≥ 5 years) 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 during a community outbreak (e.g. in case of a mismatch between circulating and vaccine strains and a pandemic situation). Zanamivir is a selective inhibitor of neuraminidase enzymes, which are glycoproteins found on the virion surface. It is active against influenza A and B. The activity of zanamivir is extracellular and is administered topically by inhalation via a diskhaler.

Intervention(s)	• Amantadine • Oseltamivir • Zanamivir
Population(s)	Adults and children who have been exposed to a clinically diagnosed case of influenza.
Standard comparators	The drugs should be compared with each other and with no prophylaxis.
Outcomes	The outcome measures to be considered include: • health-related quality of life. • mortality • cases prevented • complications prevented • hospitalisations prevented • length of influenza illness • time to return to normal activities • adverse effects of treatment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. As influenza is an acute illness which is self limiting and most complications do not carry long term sequelae a short term time horizon (e.g. yearly seasonal cycle) may be considered. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	Possible subgroups include people at higher risk of infection, severe illness and complications. High-risk groups may be further subdivided by vaccination status and consideration given to those who have not been effectively protected despite vaccination. Other factors to be considered in subgroups include • The timing of the onset of the intervention from contact • Setting of prophylaxis Other factors to be considered include • The issue of viral resistance • The duration of any prophylaxis • Extent of influenza circulating in the community Ideally, the evidence should be taken from head-to-head trials, but in their absence, a comparison of the results of different trials may be considered.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 58. February 2003. Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza. Technology Appraisal No. 67 September 2003. Guidance on the use of oseltamivir and amantadine for the prophylaxis of influenza.
Current NICE Guidance	See Addendum

Questions for consultation

The summaries of product characteristics for oseltamivir and zanamivir state that seasonal prophylaxis could be considered in exceptional situations such as a mismatch between circulation and vaccine virus strains and a pandemic situation. The guidance in TA 67 did 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.

Should the current appraisal consider prophylaxis, post exposure or seasonal, in exceptional situations? If so, which scenarios and populations would it be appropriate to evaluate the clinical and cost effectiveness seasonal prophylaxis?

Addendum. Technology Appraisal Guidance 67, issued September 2003

This guidance has been prepared in the expectation that vaccination against influenza is undertaken in accordance with national guidelines. Vaccination is the most effective way of preventing illness from influenza, and the drugs described in this guidance are not a substitute for vaccination. 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. This guidance pertains only to circumstances where it is known that either influenza A or influenza B is circulating in the community

1.1 Oseltamivir is recommended for the post-exposure prophylaxis of influenza in at-risk people aged 13 years or older who are not effectively protected by vaccination and who have been exposed to someone with influenza-like illness (ILI) and are able to begin prophylaxis within 48 hours of exposure. People who are not effectively protected by vaccination include those who have not been vaccinated since the previous influenza season, or for whom:

- vaccination is contraindicated, or has yet to take effect
- vaccination has been carried out but the vaccine is not well matched to the strain of influenza virus circulating.

(The Department of Health and the Welsh Assembly Government, acting on information from the Health Protection Agency, issue advice nationally each year on whether the vaccine and the circulating influenza virus are well matched.)

Exposure to ILI is defined as being in close contact with someone who lives in the same home environment as a person who has been suffering from symptoms of ILI.

1.2 At-risk people are defined, for the purpose of this guidance, as those who are in at least one of the following groups. People who:

- have chronic respiratory disease (including asthma and chronic obstructive pulmonary disease)
- have significant cardiovascular disease (excluding people with hypertension only)
- have chronic renal disease
- are immunocompromised
- have diabetes mellitus
- are aged 65 years or older.

1.3 Oseltamivir is recommended for the post-exposure prophylaxis of influenza in at-risk people, aged 13 years and older and who can begin prophylaxis within 48 hours, whether or not they have been vaccinated, if they live in a residential care establishment where a resident or staff member has ILI. For the purposes of this guidance, a residential care establishment is defined as a place where the at-risk person resides in the long term in order to be provided with continuing care alongside a number of other individuals.

1.4 Oseltamivir is not recommended for post-exposure prophylaxis in healthy people up to age 65 years.

1.5 Oseltamivir is not recommended for the seasonal prophylaxis of influenza.

1.6 Amantadine is not recommended for either post-exposure or seasonal prophylaxis of influenza.

1.7 Community-based virological surveillance schemes should be used to determine when influenza virus is circulating in the community. Such schemes, including those organised by the Royal College of General Practitioners and the Health Protection Agency, should ensure that the onset

of the circulation of influenza virus (A or B) within a defined area is identified as rapidly as possible.