NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Zanamivir, oseltamivir and amantadine and for the treatment of influenza (a review of existing guidance no. 58).

Draft Scope

Draft remit/appraisal objective

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

The current guidance will remain in place unless and until any new guidance has been issued. The review will consider whether any new evidence that has become available justifies a change in the original guidance.

Background

Influenza is an acute respiratory illness caused by infection with influenza A and B viruses. Influenza occurs mainly in the winter months and affects all age groups.

Influenza causes significant morbidity and increased mortality. Typical symptoms for uncomplicated influenza are cough, malaise, fever, chills, headache, nasal congestion, sore throat and aching muscles. However, symptoms can range from asymptomatic infection through respiratory illness (particularly bronchitis and pneumonia) to multi-system complications affecting the heart, lungs, brain, liver, kidneys and muscle. 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. 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.

Vaccination is currently the mainstay of influenza prevention (prophylaxis) and is recommended for the at-risk population prior to each influenza season (DOH, The Green Book, May 2007). Anti-viral drugs can also be used prophylactically. Prophylaxis may be seasonal, post-exposure or for outbreak control in residential care. NICE guidance (TA 67, September 2003) on the prophylaxis of influenza is currently being reviewed.

[1] Guidance on the use of zanamivir (review), oseltamivir and amantadine for the treatment of influenza. Technology Appraisal 58, February 2003.

The treatment of influenza is mainly supportive, consisting of alleviation of symptoms and managing any complications that may arise. NICE guidance (TA 58, February 2003) recommends using anti-viral drugs (oseltamivir and zanamivir) within their licensed indications for the treatment of influenza in at-risk patients only (see Appendix for details). The recommendations do 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.

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).

The technologies

Amantadine (Symmetrel, Lysovir, Alliance Pharmaceuticals) holds a marketing authorisation for the treatment of signs and symptoms of infection caused by influenza A virus. The SPC advises to start treatment as early as possible. When treatment is started within 48 hours of the on-set of symptoms, the duration of fever and other effects is reduced by one or two days. 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 but is not licensed for the treatment of influenza A in the Symmetrel capsule preparation.

Oseltamivir (Tamiflu, Roche) holds a marketing authorisation for the treatment of influenza in adults and children (one year of age or older) who present with symptoms typical of influenza, when influenza virus is circulating in the community. The SPC stipulates that treatment should be initiated as soon as possible within the first 48 hours of the onset of symptoms of influenza. 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. Roche are expecting to receive a license extension for two small capsule sizes for children.

Zanamivir (Relenza, GlaxoSmithKline) holds a marketing authorisation for the treatment of influenza A and B in adults and children ($\geq$ 5 years, license extension for children was granted after publication of TA 58) who present with symptoms typical of influenza when influenza is circulating in the community. Treatment should begin as soon as possible, within 48 hours after onset of symptoms for adults, and within 36 hours after onset of symptoms for children. 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 to the respiratory tract by oral inhalation only, using a Diskhaler device.

Intervention(s)	• amantadine • oseltamivir • zanamivir
Population(s)	Adults and children who present with symptoms typical of influenza, when influenza virus is circulating in the community.
Standard comparators	• oseltamivir • zanamivir • best symptomatic care
Outcomes	The outcome measures to be considered include: • incidence of influenza-related complications • incidence of hospitalisations • length of influenza illness / time to return to normal activities • mortality • adverse effects of treatment • health-related quality of life.
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	The guidance will 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. The interventions will be appraised according to their licensed indications. Guidance will only be issued in accordance with relevant marketing authorisations. Where the evidence allows, subgroups of patients with influenza who are more likely to benefit from these drugs should be identified. Possible subgroups include people at higher risk of infection, severe illness and complications. Other factors to be considered include the timing of the onset of the intervention from contact, the issue of viral resistance and the extent of influenza circulating in the community.
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.

Questions for consultation:

- Should the review of TA 58 only consider the use of these drugs for children following the license extension for zanamivir?
- Are there any reasons why it is important for the review to consider the full adult population, for example in order to redefine the 'at risk' groups?
- Are the outcome measures listed in the draft scope appropriate?

Appendix: Technology Appraisal Guidance 58, issued February 2003

This guidance has been prepared in the expectation that vaccination against influenza is undertaken in accordance with national guidance. 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 (see 1.6).

1.1 Zanamivir and oseltamivir are not recommended for the treatment of influenza in children or adults unless they are considered to be 'at risk'.

1.2 At-risk adults and children are defined for the purposes 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 old older.

1.3 Amantadine is not recommended for the treatment of influenza.

1.4 Within their licensed indications, zanamivir and oseltamivir are recommended for the treatment of at-risk adults who present with influenza-like illness (ILI) and who can start therapy within 58 hours of the onset of symptoms.

1.5 Within its licensed indications, oseltamivir is recommended for the treatment of at-risk children who present with ILI and who can start therapy within 48 hours of the onset of symptoms.

1.6 Community-based virological surveillance schemes should be used to indicate when influenza virus is circulating in the community. Community-based virological surveillance schemes, such as those

organised by the Royal College of General Practitioners and the Public Health Laboratory Service, should be used to indicate when influenza virus is circulating in the community. Such schemes should ensure that the onset of the circulation of influenza virus (A or B) within a defined area is identified as rapidly as possible.