Addendum to the review considerations for Technology Appraisal guidance on oseltamivir, zanamivir and amantadine for the prophylaxis and treatment of influenza (TA158 & TA168)

Introduction

Earlier review considerations for technology appraisal guidance 158 and 168 in November 2011 and 2013, respectively, have concluded that both should be moved to the static list. Consultees were generally supportive of the proposals.

Appendix 1 includes the recommendations of technology appraisal guidance 158 and 168 (TA158 and TA168).

Cochrane review

In April 2014 the Cochrane collaboration published its update to the systematic review for oseltamivir and zanamivir for preventing and treating influenza in healthy adults and children.

Cochrane describes the work as follows: '*We have updated and combined our reviews on the antiviral drugs zanamivir and oseltamivir for influenza in adults and children on the basis of the manufacturers' reports to regulators (clinical study reports) and the regulators' comments. We have called these comments and reports 'regulatory information'. Clinical study reports are unpublished, extensive documents with great detail on the trials that formed the basis for market approval. They include the protocols, methods and results. Clinical study reports have until now been confidential, seen only by the manufacturers and regulators*'.

A paper describing the Cochrane update, focussing on oseltamivir only, was also published in the BMJ on 9 April 2014.

Consequences for NICE guidance

We consider that the results of the Cochrane update are unlikely to change the recommendations of TA158 and TA168.

First, the population for whom oseltamivir and zanamivir are recommended by NICE is the 'at-risk' group as defined in TA158 and 168. The Cochrane update reports on evidence for healthy adults and children, without providing results for subgroups, including what could be considered as the 'at-risk' population.

Second, although the effect sizes in terms of symptomatic benefits are perhaps a little lower than was assumed in the analyses performed for NICE in TA168, they are not inconsistent with the range of estimates applied in different scenarios explored for that guidance. In those scenarios more conservative symptomatic benefits (which appear comparable to those reported here) were applied, resulting in oseltamivir as still being cost-effective.

Furthermore, 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.

Third, although it is more difficult to compare inputs for complications given the different definitions employed in the Cochrane paper and the approach used in the economic model for TA168 (i.e. linking all complications via treatment effect on antibiotic use), the results presented in the Cochrane review don't appear to be particularly different to the inputs used for TA168, and hence it is considered unlikely that this would significantly alter the conclusions.

Furthermore, excluding complications only made a difference when combined with changes to other assumptions (e.g. QoL) in the model used for TA168. In these combined scenarios, the ICER increased to >£30k in the 'otherwise healthy' population (see Tables 7.30 and 7.31 page 193 of the Assessment Group report). Importantly, these scenarios remained below £30k in the at-risk populations. These scenarios were discussed in full by the committee and their position (i.e. complications less plausible for otherwise healthy adults) is stated in paragraphs 4.3.13 - 4.3.16 of the FAD.

Finally, the Cochrane review reports an increase in adverse events of a neuropsychiatric nature in the trials for oseltamivir in adults. The Cochrane review reports that: 'in prophylaxis trials of oseltamivir there was a significant increase in patients with psychiatric adverse events over the on- and off-treatment periods (RR 1.80, 95%CI 1.05 to 3.08, I2 statistic = 0%; RD 1.06%, 95%CI 0.07 to 2.76; NNTH = 94, 95% CI 36 to 1538)'. Such a result was not reported for the treatment trials of oseltamivir or for any of the trials with zanamivir.

Although this is important new data, and potentially could be relevant to be considered in a technology appraisal, we consider it first and foremost something for the regulators to look at.

Second, it is unclear what the signal for these adverse events is in the group of interest in TA158 – 'at risk patients' – as the Cochrane review only reports on 'healthy adults' in this respect.

Third, even if this signal is exactly replicated in the at risk group, with the same intensity, and the same distribution over the various psychiatric conditions, it is difficult to be certain about the impact on the cost effectiveness of the drugs without performing the analyses. The signal is low for oseltamivir (2.20%), representing 44 events in 2000 subjects, compared with a comparably low signal for placebo (1.32% - 19 events in 1434 subjects), leading to a small difference; 0.88% in favour of placebo. Finally, it is not clear what level of severity of depression - the main event in this category – was reported for patients in these trials, although it is reported by Cochrane that of the 66 events in this category, 12 were classified as 'severe intensity' (10 oseltamivir, 2 placebo).

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Appendix

TA158

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 [1].
- 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.

[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.

TA168

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.