NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Amantadine, oseltamivir and zanamivir for the treatment of influenza (a review of NICE technology appraisal guidance 58)

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patient/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee. Where clinical specialists and patient experts make comments on the ACD separately from the organisations that nominated them, these are presented alongside the consultee comments in the tables below.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
GlaxoSmithKline	Having reviewed the ACD for the Treatment of Influenza, I can confirm that GlaxoSmithKline have no comments to make. We consider the ACD to be clear, pragmatic, and fairly reflect the evidence available surrounding the treatment of influenza.	Comment noted. No actions requested.
Roche Products	**1 Do you consider that all of the relevant evidence has been taken into account?** Roche considers that all relevant evidence has been taken into account and that a thorough analysis has been carried out for the above multiple technology appraisal.	Comment noted. No action requested.
Roche Products	**2 Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?** Roche considers that the clinical summaries and most points within the cost effectiveness summaries are reasonable interpretations of the evidence.	Comment noted. No action requested.
Roche Products	However, Roche is concerned with the wording regarding the cost-effectiveness estimates for treatment in otherwise healthy populations, stated in point 4.3.14, as follows: "*It (the Committee) considered that the most plausible presented ICERs in this group were from the scenarios exploring the combined effect of excluding hospitalisation and mortality benefits and increased GP consultation rates with a subsequent reduction in the probability that an influenza-like illness is true influenza for healthy populations. The ICERs resulting from these scenarios ranged from £18,000 to £29,000 per QALY gained in healthy adults and the Committee considered that these estimates were likely to be the lowest plausible ICERs in this population*".	Comments noted. See response below.

Consultee	Comment	Response
Roche Products	From a health economics perspective, Roche finds the wording of section 4.3.14 misleading in relation to the handling of uncertainty. The Committee appears to have made several refinements to model parameters to generate a new ICER estimate for otherwise healthy adults (i.e. combined effect of excluding hospitalisation and mortality benefits and increased GP consultation rates with a subsequent reduction in the probability that an influenza-like illness is true influenza). These revisions generated "*ICERs resulting from these scenarios from £18,000 to £29,000*" It therefore appears misleading to claim that "*these estimates were likely to be in the lowest plausible ICERs in this population*". Roche suggests a more appropriate method would be for the Appraisal Committee to agree upon a base case version of the model, given their preferences, and then utilise probabilistic sensitivity analysis (PSA) to estimate a range around the mean. Until this analysis is performed, for the Committee to claim that this particular scenario represents the "lowest plausible estimate for this population" appears to be incorrect , especially when considering that the base case estimates generated by the York assessment group took into account such parameter uncertainty. Alternatively, the list of scenarios agreed upon by the Committee may indeed represent the upper range of plausible ICERs when the uncertainty around these parameters is properly accounted for via PSA. Roche therefore requests that the Committee considers refining section 4.3.14 to provide a more appropriate representation of the likely mean and range of the ICER for otherwise healthy adults.	The ICERs of £18,000 to £29,000 in section 4.3.14 of the ACD were point estimates. The FAD has been amended to reflect the Committee's further considerations of cost effectiveness estimates in healthy populations. In healthy adults the point estimate ICERs resulting from scenarios that the Committee consider to be most plausible ranged from £39,900 to £65,000 per QALY gained. See FAD section 4.3.15.

Consultee	Comment	Response
Roche Products	**3 Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** As outlined in point 2 above, Roche is concerned that not enough consideration has been given to the fact that oseltamivir has been considered cost effective in the otherwise healthy population, as concluded by both the independent economic assessment conducted by the Assessment Group and the economic assessment conducted by Roche. Thus the provisional ACD recommendation not to recommend oseltamivir for use in the otherwise healthy adult population appears to be perverse in the light of the available evidence base made available to the Appraisal Committee.	Comment noted. See response above.
Roche Products	**4 Are there any equality related issues that may need special consideration?** Roche believes there are no equity related issues that require special considerations in this ACD.	Comment noted. No actions requested.
British Thoracic Society (comment on the Assessment Report)	This is a well written, wide ranging and balanced review of the use of anti-viral drugs for the treatment of influenza. The BTS has a few comments.	Comment noted. See detailed responses below.
British Thoracic Society (comment on the Assessment Report)	Influenza outbreaks can occur in closed communities (e.g. nursing homes and boarding schools) out of season. The use of neuraminidase inhibitors out of season in laboratory confirmed outbreaks should be permitted.	Comment noted. This has been considered by the Committee and it is recommended in the FAD that treatment with zanamivir or oseltamivir may be offered during confirmed localised outbreaks for 'at-risk' people living in long-term residential or nursing homes, see section 1.4.

Consultee	Comment	Response
British Thoracic Society (comment on the Assessment Report)	While influenza outbreaks typically occur between October and May in the UK, influenza occurs during winter and spring months in the southern hemisphere and probably all year round in equatorial regions. Tourists and other travelers could therefore present at any time of year with influenza.	Comment noted. No evidence on this situation was identified and no economic model including such a scenario was developed. Please note the context in which NICE guidance is written; health professionals are expected to take the guidance fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
British Thoracic Society (comment on the Assessment Report)	More research is required on the effectiveness of anti-viral drugs in very high risk individuals such as individuals with major immuno-suppression, and in individuals with influenza pneumonia.	Comment noted. The Committee recommended that a UK observational database should be established to monitor the effectiveness of oseltamivir and zanamivir for the treatment of influenza. See FAD section 6.1.
Diabetes UK	**Detailed response regarding points ii), iii), iv)** **ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?** It is vital that the implementation guidance that accompanies this appraisal, and the prophylaxis appraisal, both emphasise the need for awareness raising regarding the importance of the influenza vaccination as means of preventing influenza in the first instance. Whereas it is important that these technologies are available as a treatment choice where individuals have developed the flu, the availability of these technologies as potential treatment for influenza must not act as a deterrent from getting the influenza vaccination for individuals from at risk groups including people with diabetes.	Comment noted. The guidance contains a pre-amble that emphasises the importance of influenza vaccination for all people in 'at-risk' groups. See FAD pre-amble to section 1.
Diabetes UK	With regard to implementation further consideration should be given to consultation time, particularly in ensuring that the necessary screening for contraindications can be undertaken in time to enable these technologies to be prescribed.	Comment noted. The NICE implementation directorate develops support tools for implementation of NICE guidance. Your comment will be forwarded to the implementation directorate

Consultee	Comment	Response
Diabetes UK	**1.3** As outlined previously Diabetes UK particularly welcomes recommendation 1.3 that emphasises that decisions as to which technology is used are based on discussion and consider issues such as preference regarding delivery, potential adverse effects and contraindications.	Comment noted. No actions requested.
Diabetes UK	**iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** **1.1** Sufficient awareness raising must be undertaken to ensure that individuals who suspect they may have flu symptoms can attend their GP practice in time to have the necessary screening for contraindications undertaken prior to being prescribed a technology as a treatment.	Comment noted. The NICE implementation directorate develops support tools for implementation of NICE guidance. Your comment will be forwarded to the implementation directorate
Diabetes UK	**1.2** Diabetes UK welcomes the inclusion of diabetes mellitus in the list of "at risk" groups and would like to emphasise once more that this must include **all** people with diabetes including those who are treated by diet and lifestyle measures alone.	Comment noted. The Committee considered that the 'at-risk' groups were best defined in a similar way to the current recommendations for vaccination for influenza. See FAD section 4.3.2.
Diabetes UK	**1.5** The Committee has decided not to recommend amantadine having considered there was not sufficient evidence of clinical effectiveness. Diabetes UK is mindful of the above and would encourage NICE to review their position in the future in light of any further evidence or research made available. Provided it is safe and effective, and the necessary screening for contraindications has been undertaken, this technology could be an option for treatment in instances where other treatments and technologies considered in this appraisal are inappropriate or contraindicated.	Comment noted. The guidance will be considered for review in 5 years time; this includes evaluating whether any new evidence for amantadine is available.

Consultee	Comment	Response
Diabetes UK	**iv) Are there any equality related issues that may need special consideration?** **1.4** People from at risk populations residing in residential institutions must also have their needs considered. The recommendation as it currently stands does not explicitly include, for example those at risk residing in prisons, despite acknowledgement within the ACD in section 4.3.17.	The guidance does not include people living in prisons; the Committee considerations are detailed in the FAD. See FAD section 4.3.18. Please note the context in which NICE guidance is written; it represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Health professionals are expected to take the guidance fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
Diabetes UK	**General** Enabling and supporting timely access to these technologies for people without a fixed address must also be considered within the implementation guidance.	Comment noted. The NICE implementation directorate develops support tools for implementation of NICE guidance. Your comment will be forwarded to the implementation directorate
Royal College of Paediatrics and Child Health	Thank you for inviting the Royal College of Paediatrics and Child Health to comment on the above ACD. Please find our comments below. Because of licensing restrictions children under the age of 1 cannot be treated with one of the drugs and children under the age of 5 cannot be treated with the other. Because of a lack of information about effectiveness and/or side-effects in these groups 'at-risk' children may not derive potential benefit. Babies and young children with pre-existing respiratory conditions such as CF and bronchiectsis, or sickle cell disease, will not be offered drug treatment for influenza-type illnesses. Some of these children may have recently arrived in the UK and not have received immunisation. The College believes that they will therefore not have equal access to a potentially beneficial treatment.	Comment noted. Guidance can only be issued within the marketing authorisations for technologies. See Guide to the Methods of Technology section 6.1.6. The Committee considered that there was insufficient data on which to inform differential guidance on the basis of vaccination status. See FAD section 4.3.11.

Consultee	Comment	Response

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	1	No metion has been made of treatment of severe confirmed cases within 48 hours of onset outside outbreak situations.	Comment noted. No evidence on this situation was identified and no economic model including such a scenario was developed. Please note the context in which NICE guidance is written; it represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Health professionals are expected to take the guidance fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
	1	No mention of potential for resistance emerging during treatment.	Comment noted. The Committee noted that the economic models were not dynamic and could not account for potential resistance. The Committee considered that the evidence available from the submitted models was an appropriate basis on which to make a decision. See FAD section 4.3.8.
	1	Also note absence of clinical virologist on review panel.	All healthcare professional groups that are consultees or commentators are invited to nominate clinical specialists to take part in the first Appraisal Committee meeting. See the Guide to the technology Appraisal Process section 4.4.3.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.