NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA168; Amantadine, oseltamivir and zanamivir for the treatment of influenza

This guidance was issued in February 2009.

The review date for this guidance is November 2013.

1. Recommendation

TA168 should be transferred to the ‘static guidance list’.

That we consult on this proposal.

2. Original remit(s)

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

3. Current guidance

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.

4. Rationale[1]

No new clinical trial evidence was identified that would lead to a change in the recommendations of TA168. No ongoing studies that might be relevant to an update of this guidance have been identified. There are no significant concerns for the existing guidance from the 2012 work by the Cochrane Collaboration, including those explored in the context of the 2013 report by the National Audit Office and presented to the Public Accounts Committee.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January, 2008 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

the ‘Summary of evidence and implications for review’ section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

The marketing authorisations for amantadine, oseltamivir and zanamivir for the treatment of influenza have not changed since the publication of NICE technology appraisal (TA) 168 in February 2009. The manufacturers of amantadine and zanamivir have confirmed that there are no proposed extensions to the marketing authorisation of these interventions in the treatment of influenza. The manufacturer of oseltamivir confirmed that a proposed licence extension to expand the use of oseltamivir for treating children less than 1 year of age for seasonal flu is anticipated to be submitted to the [redacted].

No further technology appraisal guidance for treating influenza has been published since February 2009, suggesting no new comparator therapies have entered the market. No other guidance for treating influenza is currently scheduled in the NICE TA programme.

In NICE TA guidance 168, the Assessment Group identified 29 RCTs in its systematic review. No new evidence on the clinical effectiveness of amantadine was identified by the Assessment Group that was published after the original NICE TA guidance of amantadine, oseltamivir and zanamivir for treating influenza was issued (NICE technology appraisal guidance 58). Therefore, the Appraisal Committee concluded that it had no basis on which to change the recommendations on the use of amantadine from the original appraisal. Sixteen and 13 RCTs were identified by the Assessment Group for oseltamivir and zanamivir respectively. None of the 29 RCTs identified by the Assessment Group were head-to-head trials of oseltamivir and zanamivir. The Appraisal Committee was aware of the limitations in the evidence base for comparative efficacy of oseltamivir and zanamivir and it was not persuaded that there was evidence of differential effectiveness. The Appraisal Committee considered that oseltamivir and zanamivir, within their licensed indications, could be recommended as cost effective uses of NHS resources (see Section 3 for detailed guidance recommendations).

The literature searches did not identify any new clinical trial evidence for amantadine or inhaled zanamivir for treating people with influenza since the publication of NICE TA guidance 168. Several studies were identified investigating the use of oral zanamivir or oseltamivir by the literature searches. These studies evaluated differing treatment strategies for treating influenza (for example, dosage, treatment algorithms, combination therapies) or were comparative studies with unlicensed pharmacological agents (for example, laninamivir octanoate and peramivir). There is a still absence of phase III trial evidence directly comparing oseltamivir with zanamivir. The searches did not identify any studies that suggest the recommendations of NICE TA guidance 168 need updating or were contradicted, for example, that the treatment with oseltamivir and zanamivir in otherwise health populations would now be considered cost effective or that treatment with oseltamivir and zanamivir would no longer be consider cost effective.

The Appraisal Committee made several research recommendations in the NICE TA guidance 168 including establishing ‘a UK observational database to monitor the

effectiveness of influenza treatment with oseltamivir and zanamivir'. The literature searches did not identify any studies suggesting the research recommendations of NICE TA guidance 168 have been addressed.

None of the registered and unpublished trials presented in Appendix 2 are anticipated to address the research recommendations or change the guidance recommendations of NICE TA guidance 168. However, 1 of the studies listed in Appendix 2 is investigating an (unlicensed) intravenous formulation of zanamivir compared with oral oseltamivir in a phase III trial of adults and adolescents hospitalised with influenza (NCT01231620).

[redacted]

The current list price of amantadine (British National Formulary [BNF] 66) has reduced marginally since the publication of NICE TA guidance 168. However, this price change does not impact the recommendations of NICE TA guidance 168. The current list price of oseltamivir and zanamivir are the same as published in NICE TA guidance 168.

The clinical effectiveness evidence identified from the literature searches, registered trials and current list prices of the technologies do not suggest the recommendations of NICE TA 168 need reviewing. It is unlikely that the proposed licence extension to expand the use of oseltamivir for treating children less than 1 year of age will impact the recommendations of NICE guidance 168, given that the benefits are likely to outweigh the risks in the 'at-risk' population if the manufacturer receives regulatory approval.

Consideration has been given to the NAO report on 'Access to clinical trial information and the stockpiling of Tamiflu' that was subject to a Public Account Committee hearing in June 2013; in particular the findings of the Cochrane Collaboration intervention review into 'Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children', published in January 2012.

Cochrane focussed on reviewing clinical study reports of placebo-controlled randomised controlled trials, regulatory comments and reviews of the effects of the neuraminidase oseltamivir and zanamivir for influenza in all age groups, and appraise the trial programmes rather than single studies.

Cochrane concludes that 'oseltamivir shortens symptoms by less than a day in people with influenze-like illness (ITT population) but there is no evidence of an effect on hospitalisations', and '[however,] we found it difficult to draw hard conclusions regarding the other effects of neuraminidase inhibitors on the efficacy outcomes of key importance in this review (viral transmission and complications of influenza)'.

These conclusions are in line with those of the health technology assessments underpinning the technology appraisals in this area. Nothing has therefore materially changed in this respect as a result of the Cochrane work.

Furthermore, the health technology assessments explored the impact of inclusion and exclusion of 'complications' on the results of the economic model, leading to the

conclusion that excluding complications only made a difference when combined with changes to other assumptions in the model (e.g. QoL). 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 paras 4.3.13 - 4.3.16 of the FAD of TA168.

Based on the above information, it is proposed that TA guidance 168 is transferred to the ‘static guidance list’.

8. Implementation

A submission from Implementation is included in Appendix 3.

Data is available on the uptake of amantadine, oseltamivir and zanamivir prescribed in primary care and hospitals that have been dispensed in the community in England between July 2008 and June 2013. The ePACT data does not suggest that the use of amantadine, oseltamivir and zanamivir substantially changed after the publication of NICE technology appraisal guidance 168. However, the ePACT and Hospital Pharmacy Audit Index data suggests the use of oseltamivir and zanamivir increases during the winter months.

The use of amantadine appears to be limited in the NHS which is consistent with the non-recommendation in NICE technology appraisal guidance 168.

There is insufficient evidence to make any firm conclusions on the adherence to NICE technology appraisal guidance 168, or whether there is any regional variation in clinical practice in England and Wales.

9. Equality issues

No equality issues were raised in NICE technology appraisal guidance 168.

GE paper sign off: Janet Robertson,16 October 2013

Contributors to this paper:

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Clinical guidelines CG160 Feverish illness in children Issued: May 2013. No review date

Technology appraisals TA158 Oseltamivir, amantadine and zanamivir for the prophylaxis of influenza (including a review of TA67) Issued: September 2008. Reviewed: November 2011 – it was decided the guidance should be transferred to the 'static guidance list'

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Osetamivir (Roche) In patients one year of age and older who present with symptoms typical of influenza, when influenza virus is circulating in the community	To expand the use of oseltamivir into treatment of children less than one year of age for seasonal flu. [redacted]
Zanamivir (GlaxoSmithKline)	Aqueous solution formulation for intravenous administration. [redacted]

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Nitazoxanide for acute uncomplicated influenza	

Registered and unpublished trials

Trial name and registration number	Details
A Phase III International, Randomized, Double-blind, Double-dummy Study to Evaluate the Efficacy and Safety of 300 mg or 600 mg of Intravenous Zanamivir Twice Daily Compared to 75 mg of Oral Oseltamivir Twice Daily in the Treatment of Hospitalized Adults and Adolescents With Influenza (NCT01231620)	Estimated enrolment: 462 Estimated study completion date: February 2015
A Randomised Controlled Trial on the Effect of Post-exposure Oseltamivir Prophylaxis on Influenza Transmission in Nursing Homes (NCT01053377)	Estimated enrolment: 900 Estimated study completion date: December 2013
A Double-blind, Randomized, Stratified Multi-center Trial Evaluating Conventional and High Dose Oseltamivir in the Treatment of Immunocompromised Patients With Influenza (NCT00545532)	Estimated enrolment: 166 Estimated study completion date: January 2015
Efficacy of Early Oseltamivir Phosphate Treatment at Hospital Admission to Reduce Severity of Illness Among Children Aged Less Than 10 Years Hospitalized With Influenza in El Salvador and Panama (NCT01690637)	Estimated enrolment: 1400 Estimated study completion date: December 2013
Comparative Clinical Trial of Efficiency and Safety of Ergoferon Versus Oseltamivir in Treatment of Influenza (NCT01850446)	Estimated Enrolment: 150 Estimated Study Completion Date: June 2015
Effectiveness of Empiric Antiviral Treatment for Hospitalized Community Acquired Pneumonia During the Influenza Season (U18) (NCT01248715)	Estimated Enrolment: 1000 Estimated Study Completion Date: May 2014
Multicentre Open Label Comparative Parallel-group Randomized Clinical Trial of Clinical Efficiency and Safety of Ergoferon in Treatment of Influenza (NCT01804946)	Estimated Enrolment: 370 Estimated Study Completion Date: August 2015

Appendix 3 – Implementation submission

Review of NICE Technology Appraisal guidance No. 168; Amantadine, oseltamivir and zanamivir for the treatment of influenza

Please contact Rebecca Braithwaite regarding any queries
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Contents

1. Routine healthcare activity data

1.1. ePACT data

This section presents electronic prescribing analysis and cost tool (ePACT) data on the net ingredient cost (NIC) and volume of Amantadine, Oseltamivir and Zanamivir prescribed in primary care and hospitals that has been dispensed in the community in England between July 2008 and June 2013.

Figure 1 Cost and volume of Amantadine dispensed in the community in England.

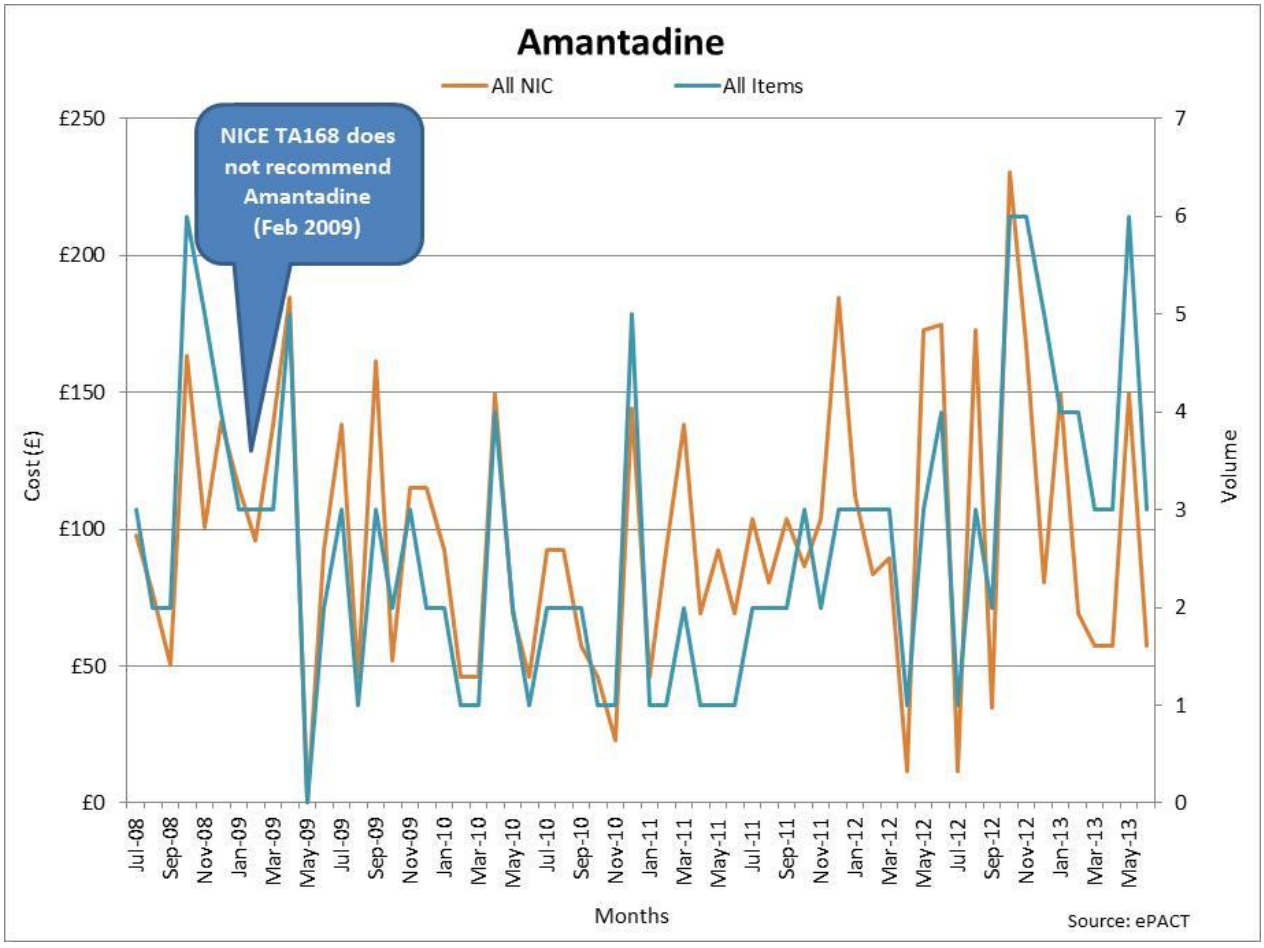


Figure 2 Cost and volume of Oseltamivir dispensed in the community in England.

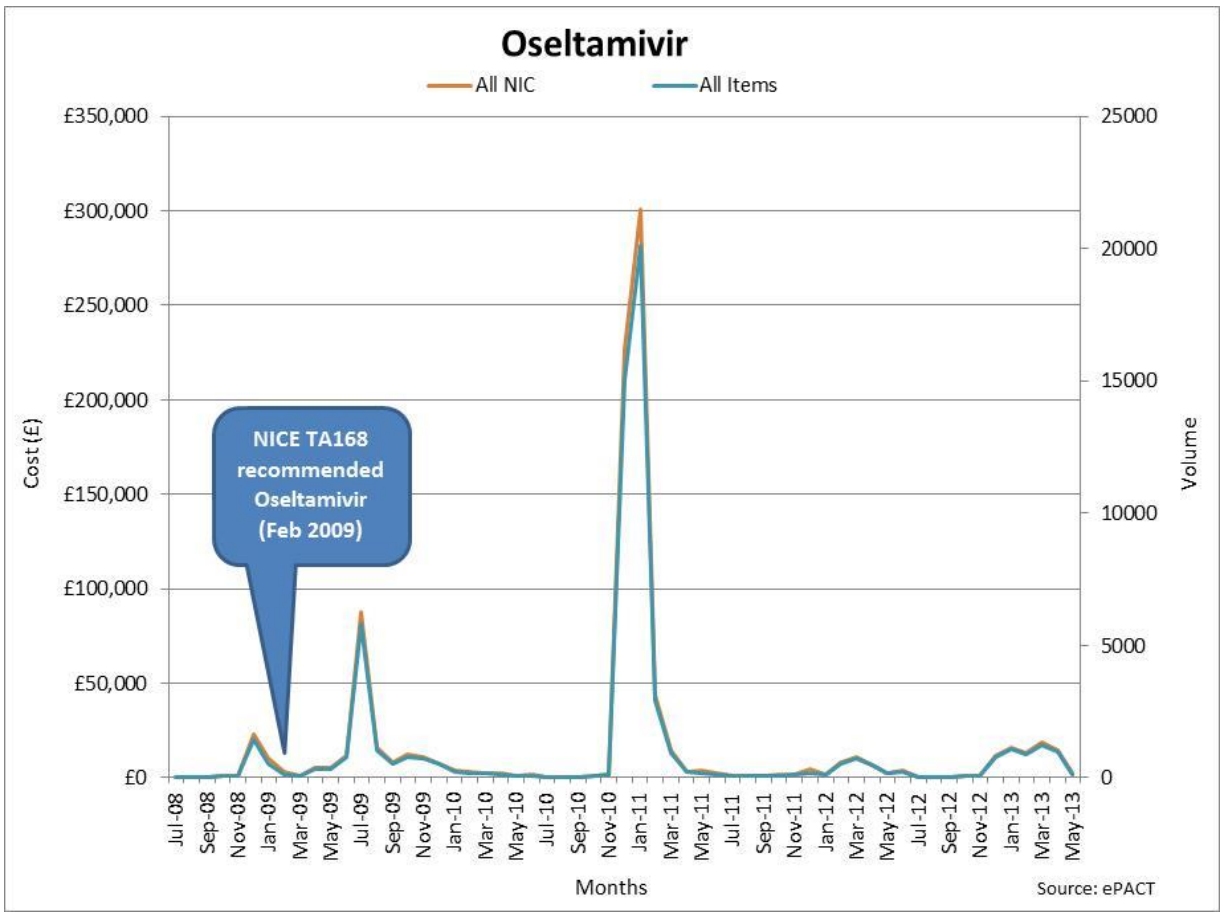
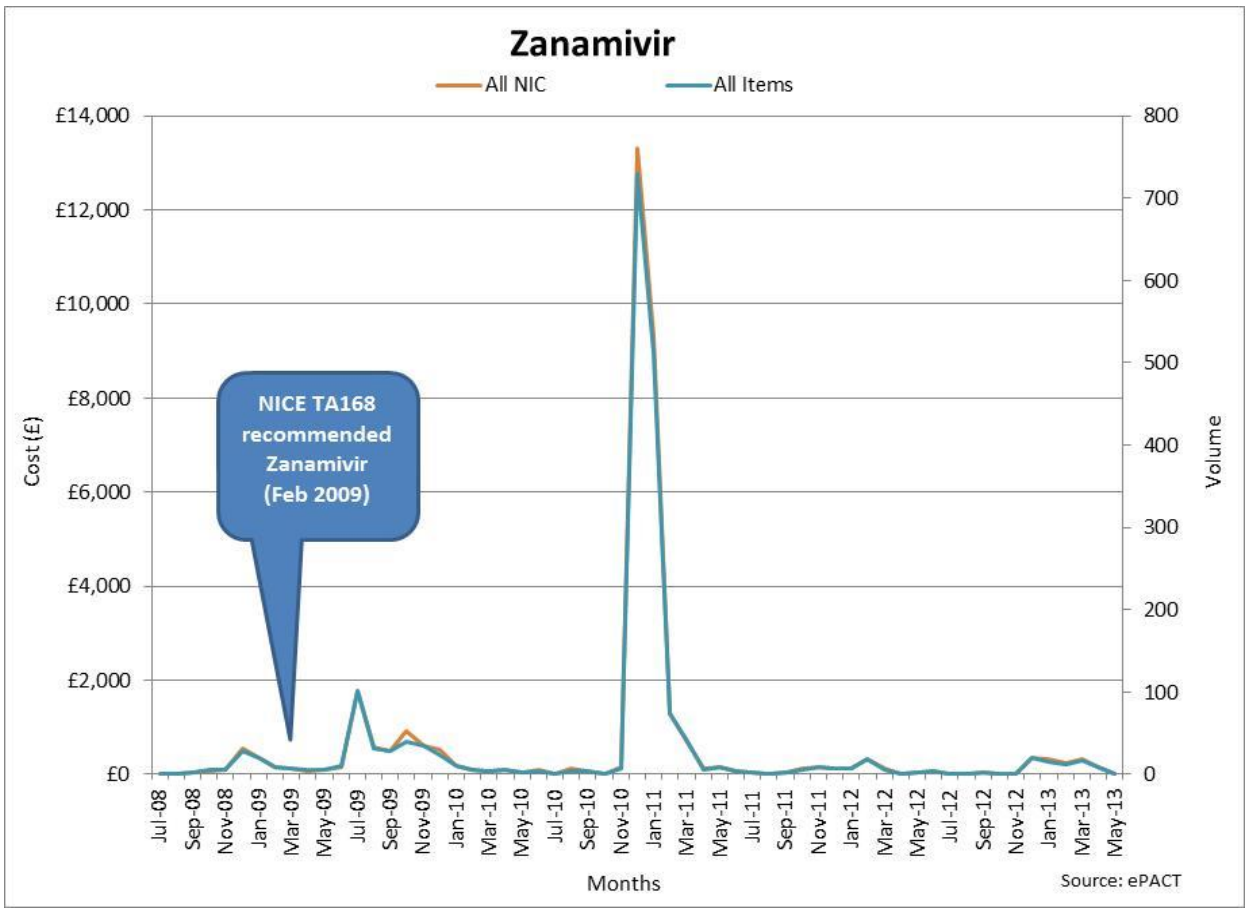


Figure 3 Cost and volume of Zanamivir dispensed in the community in England.



1.2. Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index data on the net ingredient cost (NIC) and volume of Amantadine, Oseltamivir and Zanamivir prescribed and dispensed for use in hospitals in England during 2012.

Figure 4 Cost and volume of Amantadine prescribed and dispensed for use in hospitals in England

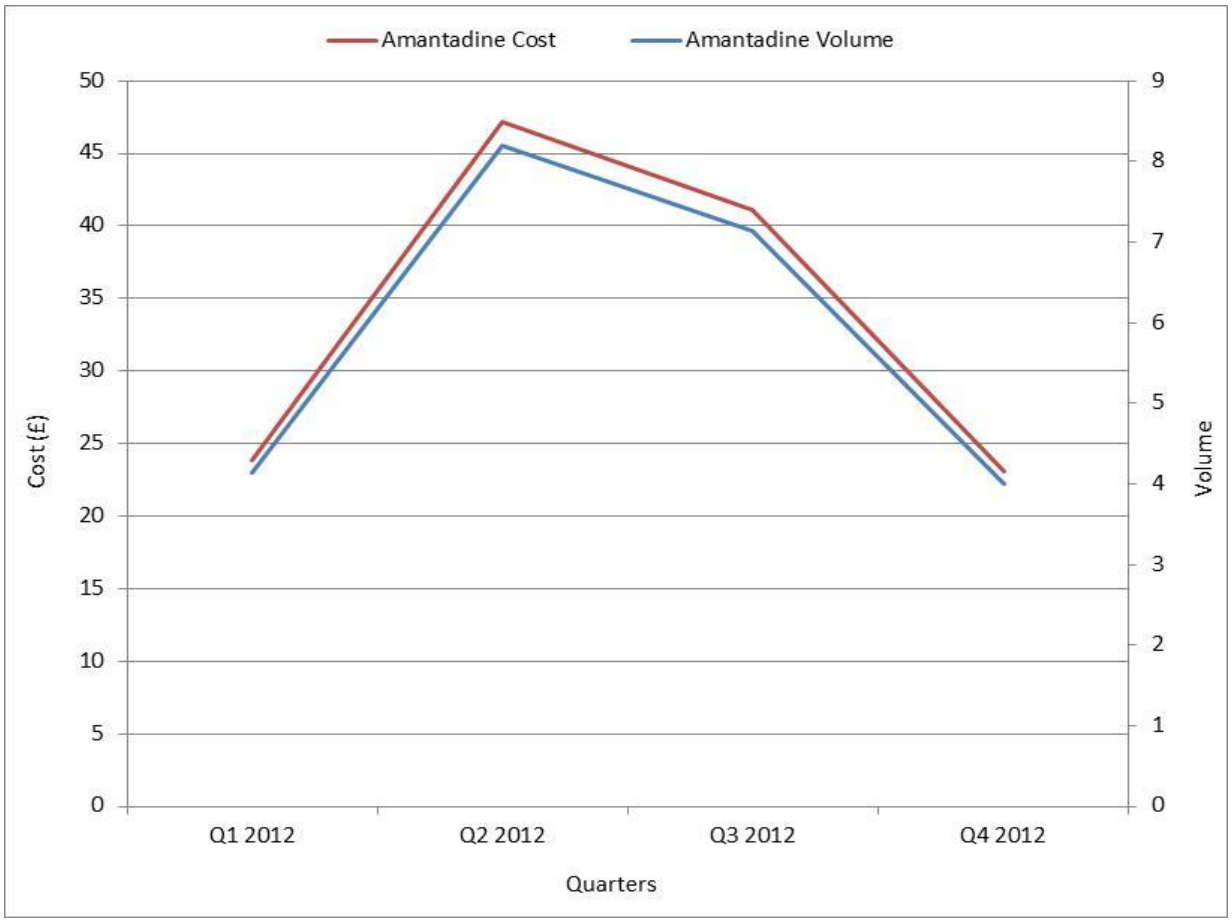


Figure 5 Cost and volume of Oseltamivir prescribed and dispensed for use in hospitals in England

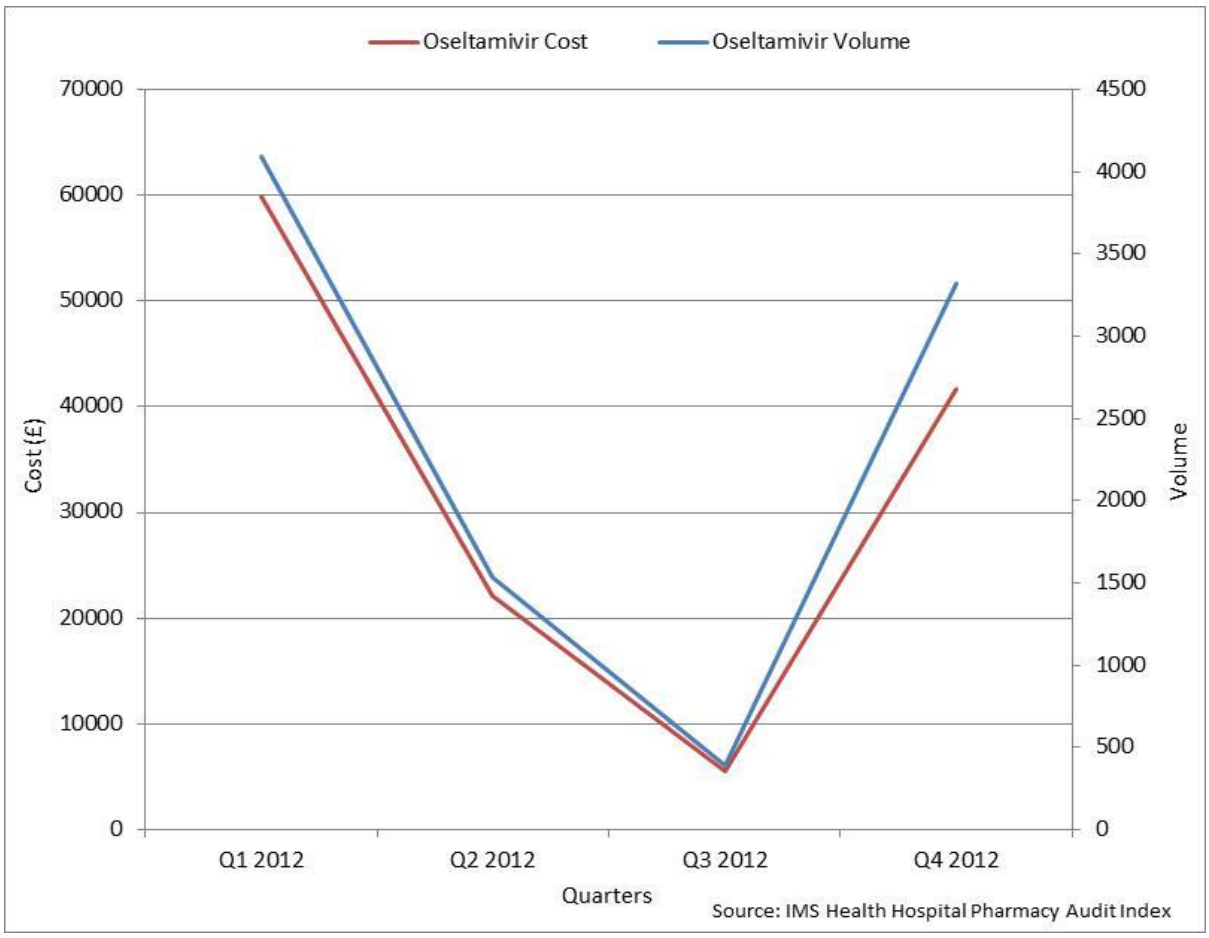
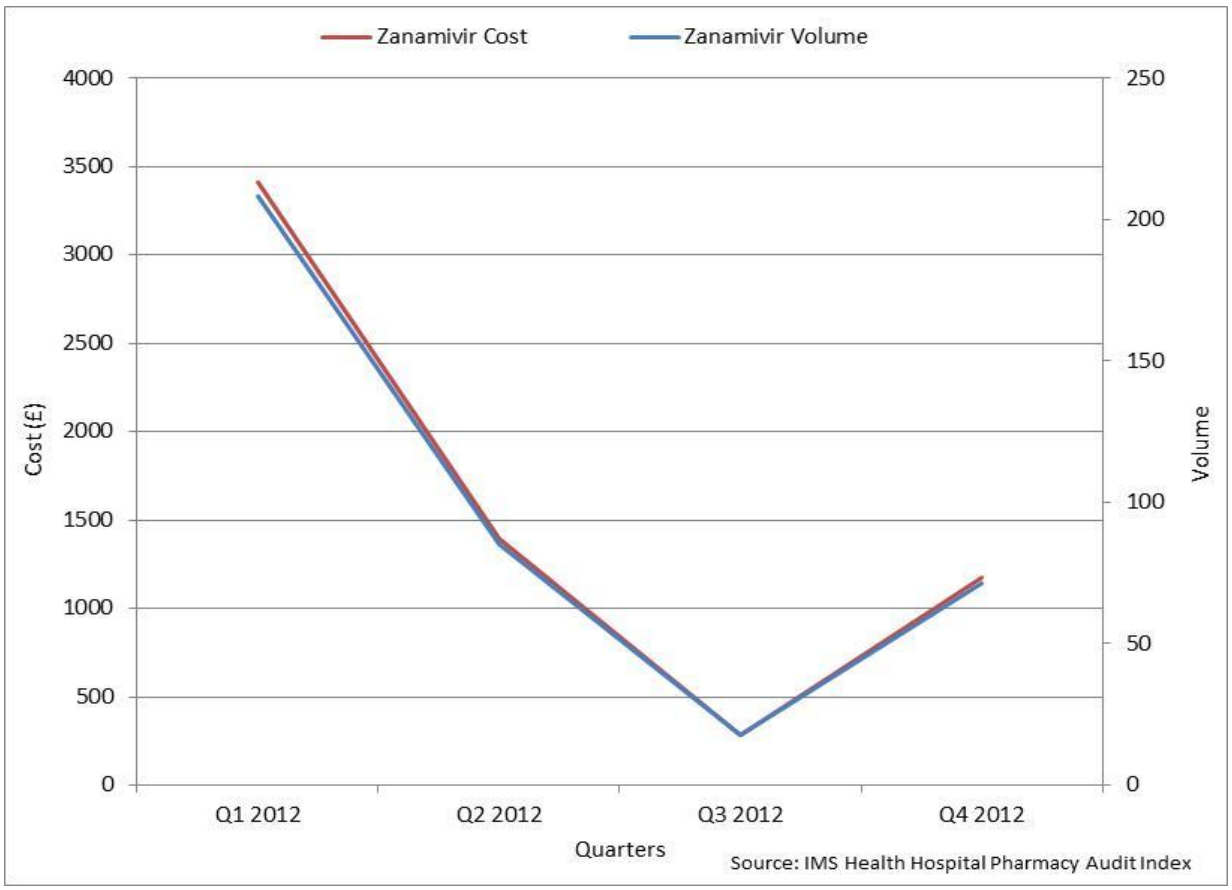


Figure 6 Cost and volume of Zanamivir prescribed and dispensed for use in hospitals in England



2. Implementation studies from published literature

Information is taken from the uptake database website.

Nothing specific to add.

3. Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing specific to add.

Appendix A: Healthcare activity data definitions

ePACT

Prescribing analysis and cost tool system

This information comes from the electronic prescribing analysis and cost tool (ePACT) system, which covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Services Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions written in hospitals but dispensed in the community (FP10 [HP]) are not included in PACT data. Prescriptions dispensed in hospitals or mental health units, and private prescriptions, are not included in PACT data.

Measures of prescribing

Prescription Items: Prescriptions are written on a prescription form. Each single item written on the form is counted as a prescription item. The number of items is a measure of how many times the drug has been prescribed.

Cost: The net ingredient cost (NIC) is the basic price of a drug listed in the drug tariff, or if not in the drug tariff, the manufacturer's list price.

Data limitations (national prescriptions)

PACT data do not link to demographic data or information on patient diagnosis. Therefore the data cannot be used to provide prescribing information by age and sex or prescribing for specific conditions where the same drug is licensed for more than one indication.

IMS HEALTH Hospital Pharmacy Audit Index

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies: to wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The

estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.