NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA223; Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease.

This guidance was issued in May 2011.

The review date for this guidance is May 2014.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

To appraise the clinical and cost effectiveness of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate within their licensed indications for the treatment of intermittent claudication in people with peripheral arterial disease.

3. Current guidance

1.1 Naftidrofuryl oxalate is recommended as an option for the treatment of intermittent claudication in people with peripheral arterial disease for whom vasodilator therapy is considered appropriate after taking into account other treatment options. Treatment with naftidrofuryl oxalate should be started with the least costly licensed preparation.

1.2 Cilostazol, pentoxifylline and inositol nicotinate are not recommended for the treatment of intermittent claudication in people with peripheral arterial disease.

1.3 People currently receiving cilostazol, pentoxifylline and inositol nicotinate should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

4. Rationale[1]

No changes to the marketing authorisation, drug prices or the evidence have been identified that would lead to a change in the recommendations of the original guidance. No ongoing studies have been identified that would satisfy the research recommendation in the guidance. It is therefore proposed that the guidance is placed on the static list.

[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

5. Implications for other guidance producing programmes

This TA overlaps with CG147 Lower Limb Arterial Disease published in August 2012. The clinical guideline included a review that looked at the sequence of Naftidrofuryl oxalate in comparison to other interventions such as supervised and non-supervised exercise, angioplasty and by-pass surgery.

CCP supports the decision to transfer the TA to the static list. The clinical guideline's 2 year evidence update review will be completed in November 2014.

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 March 2009 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 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 list prices for the interventions that were not recommended in TA223 (cilostazol, pentoxifylline, inositol nicotinate) have not changed or only slightly changed. However, naftidrofuryl oxalate, which was recommended in TA223, now has an increased generic price (from £4.52 to £6.27). However, the sensitivity analyses conducted during TA223 which used the branded price (£8.10) led to ICER that were also accepted by the Appraisal Committee as cost effective. Therefore, the increased price of naftidrofuryl oxalate is not expected to impact on the current recommendations.

The marketing authorisations for naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for use in peripheral arterial disease have not changed since the publication of the guidance. However, the marketing authorisation for cilostazol has been updated to include the following wording:

> "*Pletal is for second-line use, in patients in whom lifestyle modifications (including stopping smoking and [supervised] exercise programs) and other appropriate interventions have failed to sufficiently improve their intermittent claudication symptoms."*

This follows a CHMP recommendation in March 2013 that *"cilostazol should only be used in patients whose symptoms have not improved despite prior lifestyle changes such as exercise, healthy diet and stopping smoking."*

However, this amendment does not impact on the recommendations in the current guidance.

No new treatments have come to market since the publication of technology appraisal. However, a study of the effects of ramipril on walking times in people with peripheral arterial disease was recently published (Kurlinsky and Levy, 2013). The study contained 212 patients and showed improvements in walking times compared with placebo. Ramipril does not have a marketing authorisation in the UK for this indication.

TA223 included the following research recommendation: *'A trial comparing the long-term effectiveness (beyond 24 weeks) of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate and placebo would be beneficial. It should collect utility data as well as walking distance outcomes.* ' No ongoing study addressing this research questions was identified.

Two ongoing studies were identified (see page 10), one of which evaluates surgical interventions and is outside the remit of this appraisal. The second one (NCT01711333) is a phase IV study and plans to investigate cilostazol in peripheral arterial disease due to chronic occlusive arterial disease. Although the completion date is stated as September 2014, it is not yet open for recruiting, and no other information about the trial is available.

No other relevant published clinical trials assessing the efficacy and safety of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate were identified in the literature searches, and the manufacturers of these technologies were not aware of any new available evidence since the publication of this technology appraisal.

8. Implementation

A submission from Implementation is included in Appendix 3.

Based on the implementation advice in Appendix 3, the prescriptions of naftidrofuryl oxalate appear to have increased and been maintained since publication of the guidance in May 2011, while the consolidated prescription data for cilostazol, pentoxifylline and inositol nicotinate suggest that prescriptions for these medicines has decreased. However as noted in Appendix 3 these data need to be treated with caution as these medicines have more than one licensed indication. Overall, the available prescribing data suggest that NICE guidance is being adhered to.

9. Equality issues

No issues had been highlighted during the course of the appraisal. The Committee was aware that the prevalence of peripheral arterial disease differs between ethnic groups, but concluded that the recommendations do not affect access to the technology for any specific groups.

GE paper sign off: Elisabeth George, Associate Director, 07 04 2014

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 to [specify date or trial].	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 Guideline CG147 Lower limb peripheral arterial disease: Diagnosis and management. Issue date: August 2012.

Technology Appraisal TA210 Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of NICE technology appraisal guidance 90). Issue date: December 2010. Review decision December 2013: transfer to static guidance.

Quality Standard QS52 Peripheral arterial disease. Issue date: January 2014.

NICE Pathway Lower limb peripheral arterial disease. Created August 2012. Last updated January 2014.

Details of changes to the indications of the technology

Indication considered in original appraisal	**Proposed indication (for this appraisal)**
"Cilostazol has a UK marketing authorisation for the 'improvement of the maximal and pain-free walking distances in patients with intermittent claudication, who do not have rest pain and who do not have evidence of peripheral tissue necrosis'."	The SPC also now says specifically: *"Pletal is for second-line use, in patients in whom lifestyle modifications (including stopping smoking and [supervised] exercise programs) and other appropriate interventions have failed to sufficiently improve their intermittent claudication symptoms."* This follows a CHMP recommendation in March 2013 that *"cilostazol should only be used in patients whose symptoms have not improved despite prior lifestyle changes such as exercise, healthy diet and stopping smoking."* The CHMP statement also says: *"The recommendations follow a review of current evidence which indicates that the modest benefits of these medicines, i.e. their ability to increase the distance patients are able to walk, are only greater than their risks, in particular the risks of side effects affecting the heart or serious bleeding, in a limited subgroup of patients."*
Naftidrofuryl oxalate, pentoxifylline and inositol nicotinate have the same indication currently as that listed in TA223.	

Registered and unpublished trials

Trial name and registration number	Details
A Multicenter, Therapeutic Used Study to Evaluate the Efficacy and Safety of Pletaal SR Capsule (Cilostazol) in Subjects With Peripheral Arterial Disease Symptom Due to Chronic Occlusive Arterial Disease. NCT01711333	Phase IV, not yet open for recruiting. Estimated enrolment: 100 Primary completion date: September 2014.
Comparative Effectiveness Research Study of Peripheral Arterial Disease (PAD) NCT01378260	Observational study (no phase given), ongoing not recruiting, to test the following hypotheses (where the medical management is cilostazol or pentoxifylline): Hypothesis 1: At 12-months, surgical interventions are associated with greater improvements in function, claudication symptoms, and health-related quality of life (HRQoL) than endovascular procedures or medical management. Hypothesis 2: At 12-months, surgical and endovascular interventions are associated with greater improvements in function, claudication symptoms, and HRQoL than medical management. Estimated enrolment: 1100 Primary completion date: September 2014.

References

Kurlinsky AK and Levy M. (2013) Effect of ramipril on walking times and quality of life among patients with peripheral artery disease and intermittent claudication: a randomized controlled trial. *Journal of the American Medical Association* 309: 453-460

Appendix 3 – Implementation submission

Review of NICE technology appraisal guidance No. 223; Peripheral arterial disease - cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate

Please contact Leighton Coombs 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 naftidrofuryl, cilostazol, pentoxifylline and inositol nicotinate prescribed in primary care and in hospitals and dispensed in the community in England between April 2009 and December 2013. These data need to be treated with caution as these medicines have more than one licensed indication. Cilostazol, pentoxifylline and inositol nicotinate were not recommended in TA223 and so their prescribing data has been consolidated and is presented separately.

Figure 1 Cost and volume of naftidrofuryl prescribed in primary care and hospitals that have been dispensed in the community in England

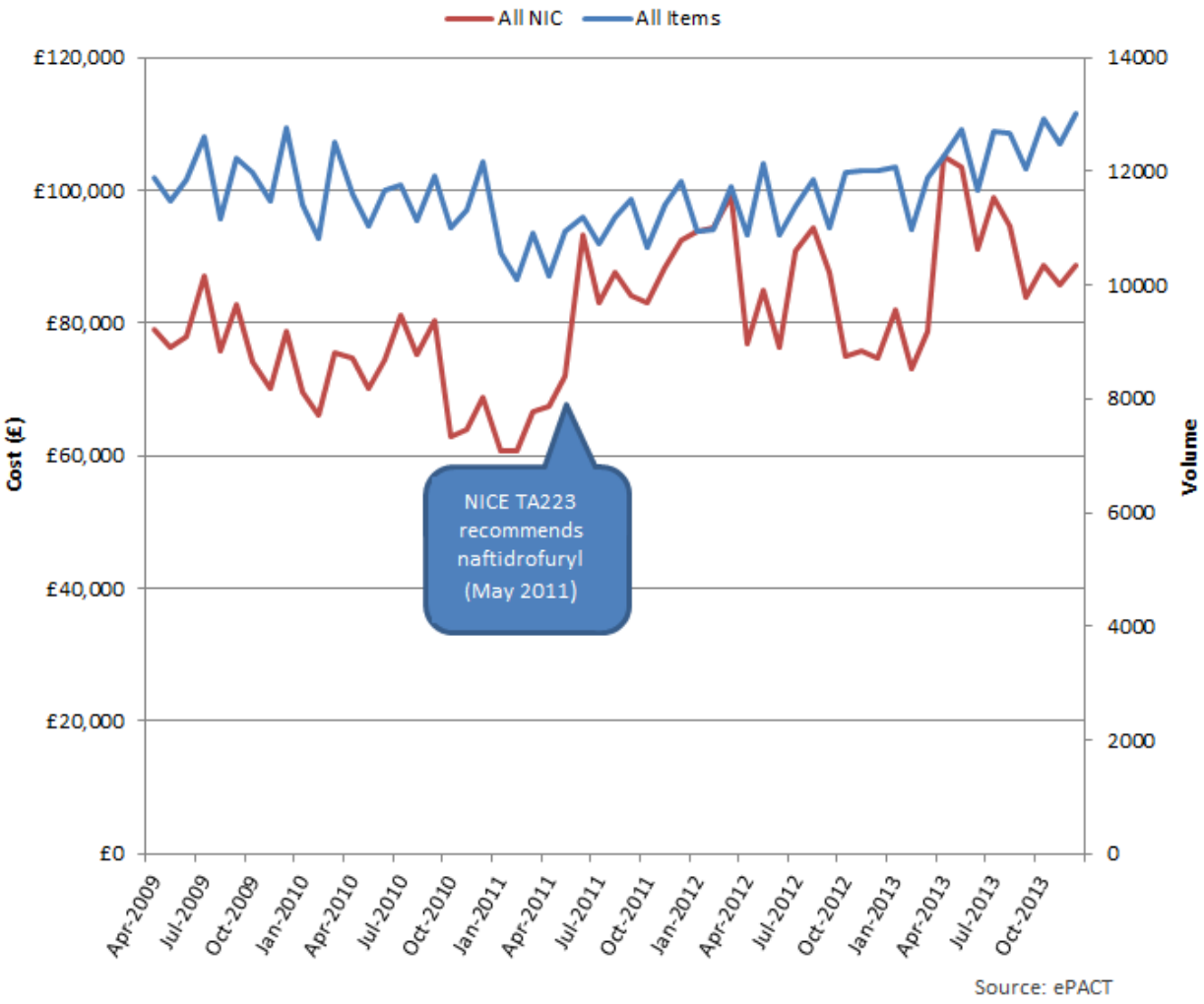
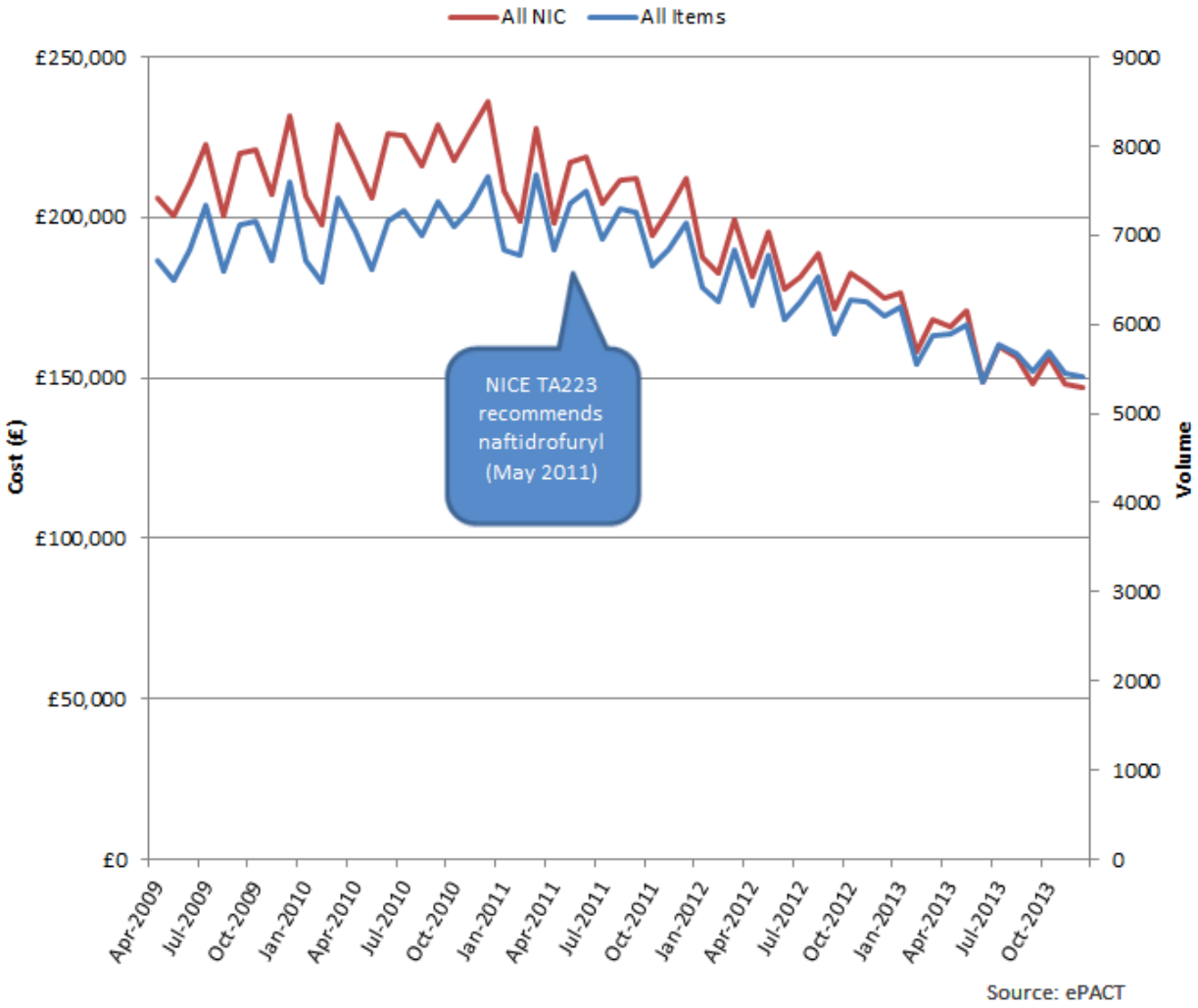


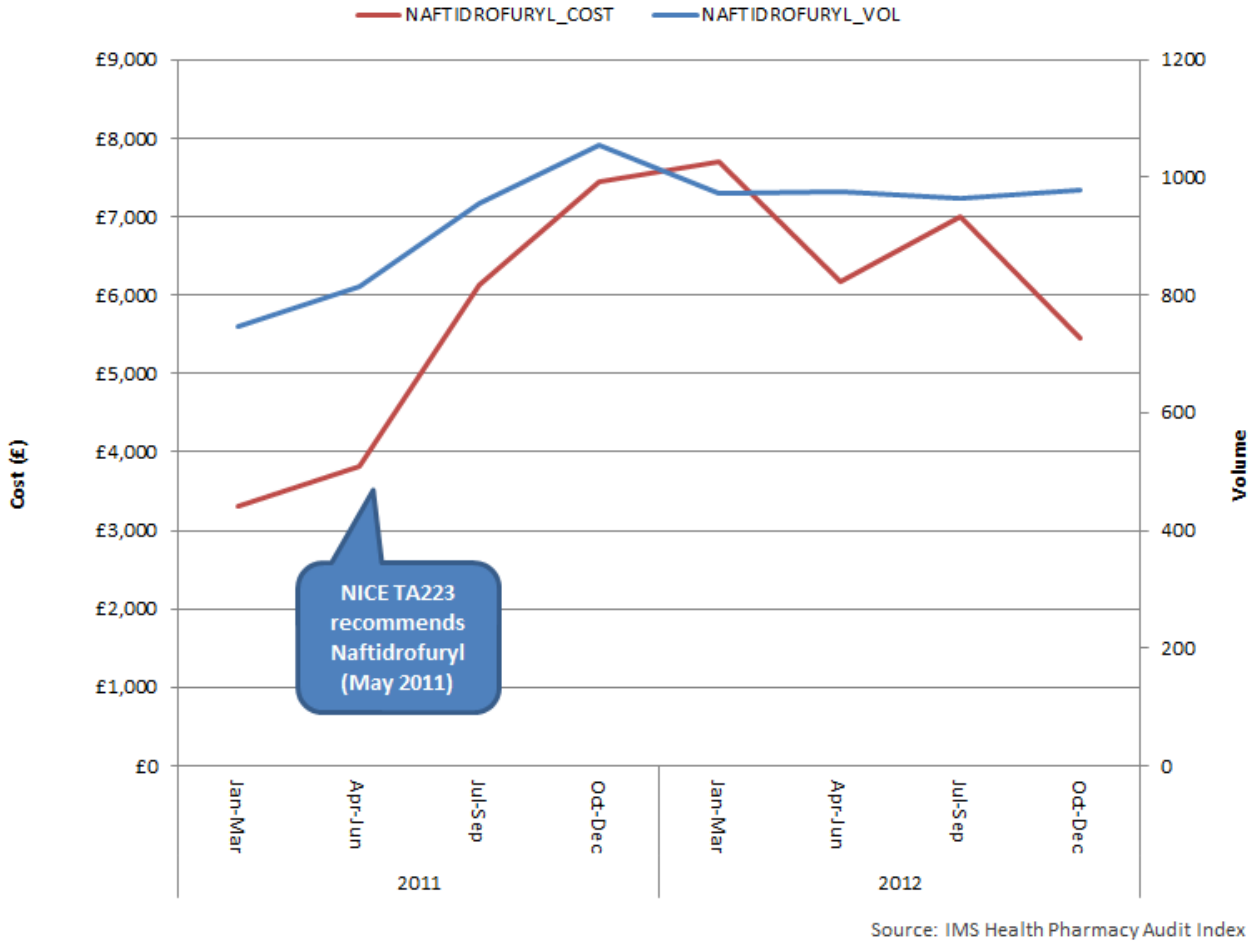
Figure 2 Cost and volume of cilostazol, pentoxifylline and inositol nicotinate prescribed in primary care and hospitals that have been dispensed in the community in England



Hospital Pharmacy Audit Index data

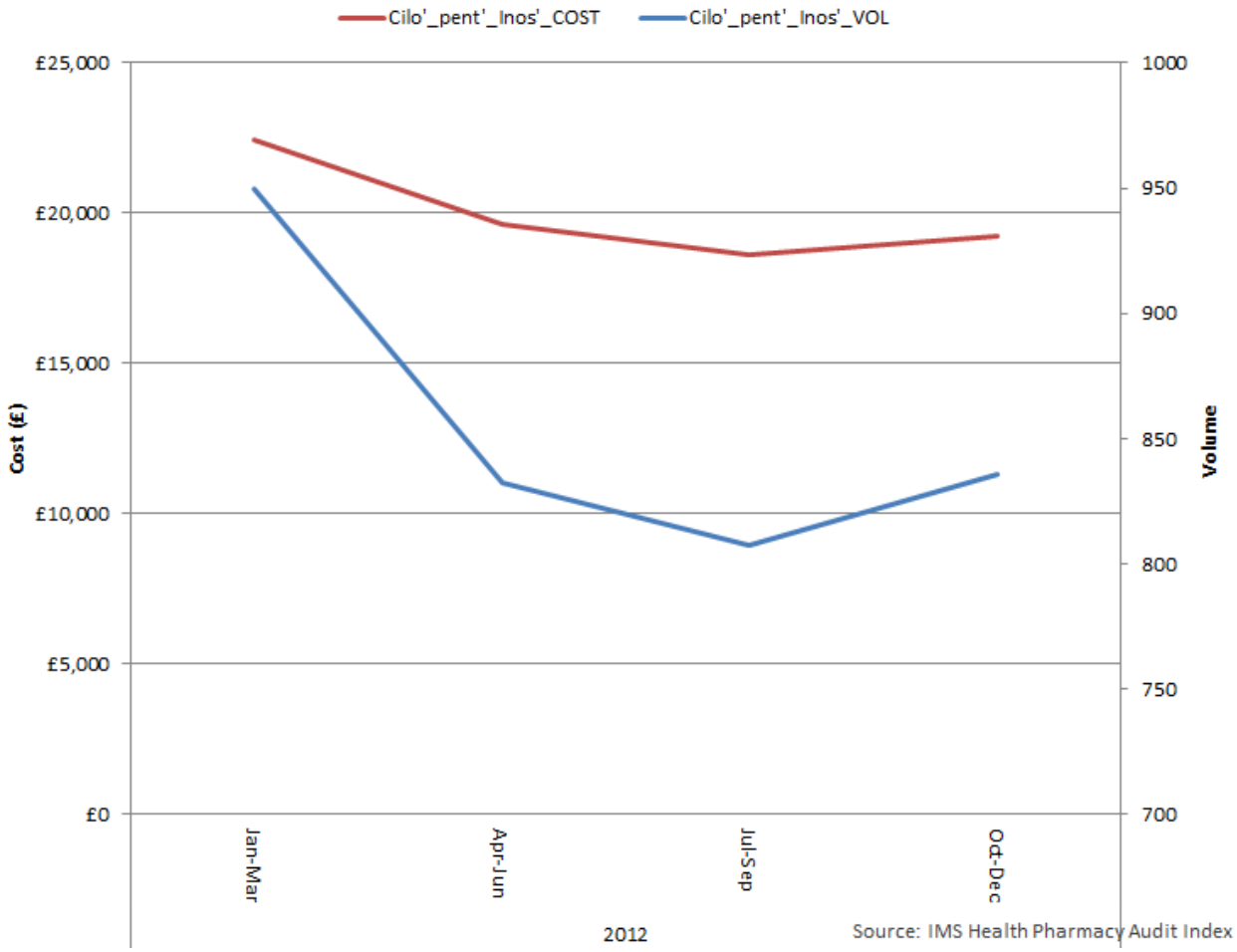
This section presents Hospital Pharmacy Audit Index (HPAI) data on the net ingredient cost (NIC) and volume of naftidrofuryl prescribed and dispensed in hospitals in England between January 2011 and December 2012. Data for cilostazol, pentoxifylline and inositol nicotinate are presented on the same basis for the period covering January 2012 to December 2012. These data need to be treated with caution as these medicines have more than one licensed indication.

Figure 3 Cost and volume of naftidrofuryl prescribed in hospitals in England



Source: IMS Health Pharmacy Audit Index

Figure 4 Cost and volume of cilostazol, pentoxifylline and inositol nicotinate prescribed in hospitals in England



Implementation studies from published literature

Nothing to report for these TAs from the uptake database website.

Qualitative input from the field team

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

Nothing to report at this stage

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 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.