NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA70; Guidance on the use of imatinib for chronic myeloid leukaemia, and TA251; Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia

This guidance was issued in October 2003 (TA70) and April 2012 (TA251).

The review date for TA251 is May 2014. In July 2009, the decision was made to update TA70. Recommendation 1.1 from TA70 has been updated by TA251. Recommendation 1.3 from TA70 has been updated by TA241 (January 2012).

1. Recommendation

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

2. Original remit(s)

TA70: *"To advise on the clinical and cost-effectiveness of imatinib (Glivec), relative to existing treatments, in its licensed indications for the first line treatment of chronic myeloid leukaemia"*.

TA251: *"To appraise the clinical and cost effectiveness of dasatinib, nilotinib and standard-dose imatinib within their licensed indications for the first-line treatment of chronic myeloid leukaemia (including part-review of TA70)".*

3. Current guidance

TA70

1.1 This recommendation has been updated and replaced by NICE technology appraisal guidance 251.

1.2 Imatinib is recommended as an option for the treatment of people with Philadelphia-chromosome-positive CML who initially present in the accelerated phase or with blast crisis. Additionally, imatinib is recommended as an option for people who present in the chronic phase and then progress to the accelerated phase or blast crisis if they have not received imatinib previously.

1.3 This recommendation has been updated and replaced by NICE technology appraisal guidance 241.

1.4 For people in chronic-phase CML who are currently receiving interferon alpha (IFN-α) as first-line treatment, the decision about whether to change to imatinib should be informed by the response of the disease to current treatment and by

the tolerance of the person to IFN-α. This decision should be made after informed discussion between the person with CML and the clinician responsible for treatment, taking full account of the evidence on the risks and benefits of imatinib and the wishes of the person

TA251

1.1 Standard-dose imatinib is recommended as an option for the first-line treatment of adults with chronic phase Philadelphia-chromosome-positive chronic myeloid leukaemia (CML).

1.2 Nilotinib is recommended as an option for the first-line treatment of adults with chronic phase Philadelphia-chromosome-positive CML if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme.

1.3 Dasatinib is not recommended for the first-line treatment of chronic phase Philadelphia-chromosome-positive CML.

1.4 People currently receiving dasatinib that is not recommended according to 1.3 should be able to continue treatment until they and their clinician consider it appropriate to stop

4. Rationale[1]

The new follow-up data is unlikely to lead to a change in the recommendations of the original guidance. There are currently no changes in the costs of these drugs, and generic imatinib will not be available for some time. Therefore we propose that the guidance should be transferred to the 'static guidance list'.

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 March 2009 (TA70 recommendations only) and May 2011 (TA251 recommendations) 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

[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

Two extensions to the marketing authorisation for dasatinib are planned [redacted]. There are no planned changes to the marketing authorisations of imatinib or nilotinib relating to TA251.

TA251 (section 4.3.20) states 'The Committee further concluded that the recommendations for first-line tyrosine kinase inhibitors should be considered for review in 2 years' time when the price of standard-dose imatinib may be affected by the entry of new manufacturers.' This statement implies that there was an expectation that generic imatinib would be available in 2014 or 2015. However, the manufacturer has stated that the patent expiry for imatinib is not due until June 2016 at the earliest [redacted].

The cost of dasatinib is unchanged from that in TA251 (i.e. £2504.96 for a pack of 30 100 mg tablets). TA251 states that 'The Committee concluded that the ICERs for dasatinib were substantially outside the range normally considered a cost-effective use of NHS resources'. The costs of imatinib (£1724.39 for a 400 mg 30-tablet pack) and nilotinib (£2432.85 for a 150 mg 112-tablet pack) have also remained unchanged from TA251. No changes have been made to the patient access scheme set up for nilotinib since the publication of TA251, and it is the manufacturer's intention that the scheme will remain unchanged.

New long term follow-up data have become available for nilotinib and dasatinib since the previous appraisal. These include up follow-up data for dasatinib compared with imatinib in the DASISION trial, and follow-up data for nilotinib compared with imatinib in the ENESTnd and ENESTcmr trials. These data maintain the demonstrated clinical benefit of nilotinib and dasatinib over imatinib. The Committee for TA251 concluded that 'there was insufficient evidence to distinguish between dasatinib and nilotinib in terms of clinical effectiveness', as there were no trials directly comparing the two treatments: there are still no trials directly comparing dasatinib with nilotinib.

With no changes to the costs of the interventions, the new follow-up data is unlikely to lead to a change in the recommendations of the original guidance.

8. Implementation

A submission from Implementation is included in Appendix 3.

The volume and cost of imatinib and nilotinib prescribed in primary care and in hospitals and dispensed in the community fluctuated – with a slight decrease in volume and cost for imatinib and a slight increase in volume and cost for nilotinib in the months following the publication of TA241 and TA251. Hospital Pharmacy Audit Index (HPAI) data indicated increased volume and cost of imatinib and nilotinib prescribed in hospitals in England in the months following the publication of TA251; however, data for nilotinib were not available before this time so it is not possible to determine the effect of publication. In addition, these data do not link to diagnosis and so should be treated with caution.

9. Equality issues

No equality issues were identified.

GE paper sign off: Elisabeth George, Associate Director, 04 08 2014

Contributors to this paper:

Information Specialist:	Tom Hudson
Technical Lead:	Chris Chesters
Implementation Analyst:	Rebecca Braithwaite
Project Manager:	Andrew Kenyon

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 April 2016	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

Bosutinib for previously treated chronic myeloid leukaemia. NICE Technology Appraisal TA299. Issued: November 2013. Review date: July 2016.

Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance. NICE Technology Appraisal TA241. Issued: January 2012. Review date: September 2014.

Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia. NICE Technology Appraisal TA218. Issued: March 2011. Review date: February 2014. The review proposal recommended that this appraisal is moved to the list of static guidance.

Referred - QSs and CGs

Haematological malignancies. NICE Quality Standard (referred).

Suspended/terminated

Decitabine for the treatment of acute myeloid leukaemia. NICE Technology Appraisal TA270. Issued: December 2012. Terminated as no evidence submission was received from the manufacturer.

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Imatinib Treatment of adult and paediatric patients with: newly diagnosed Philadelphia-chromosome (*BCR-ABL*) positive CML for whom bone marrow transplantation is not considered as the first line of treatment Philadelphia-chromosome-positive CML in chronic phase after failure of interferon alfa therapy or in accelerated phase or blast crisis.	No change.

Indication considered in original appraisal	Proposed indication (for this appraisal)
Dasatinib Treatment of: • Adult patients with newly diagnosed Philadelphia-chromosome-positive chronic myelogenous leukaemia in the chronic phase. • Adult patients with chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesilate.	The manufacturer has informed NICE of a proposed license extension [redacted].
Nilotinib Treatment of: • Adult patients with newly diagnosed Philadelphia-chromosome-positive chronic myelogenous leukaemia (CML) in the chronic phase. • Adult patients with chronic phase and accelerated phase Philadelphia-chromosome-positive CML with resistance or intolerance to prior therapy including imatinib.	No change.

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
Bosutinib (Pfizer)	Phase III for first-line treatment of Philadelphia-chromosome-positive CML
Imatinib biosimilar (Teva)	Approved in the EU for: • Paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment. • Paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis. • Adult patients with Ph+ CML in blast crisis. Note that Novartis' existing patent protection means

Drug (manufacturer)	Details (phase of development, expected launch date,)
	that any imatinib biosimilars are unlikely to be available on the European market before June 2016 at the earliest.

Registered and unpublished trials

Trial name and registration number	Details
Safety and Efficacy of Nilotinib vs. Imatinib in the Treatment of Newly Diagnosed Chinese Ph+ CML-CP Patients NCT01275196; MACS1346; CAMN107ECN02.	N = 264 Estimated completion date: September 2014
Efficacy and Safety of Nilotinib Patients With Newly Diagnosed CML - CP (Chronic Myelogenous Leukemia - Chronic Phase) NCT00718263; PHCHBS-WD4070; CAMN107A2303E1.	Nilotinib vs. imatinib N = 90 Estimated primary completion date: May 2018.
Comparison of Imatinib Versus Dasatinib in Patients With Newly-diagnosed Chronic Phase Chronic Myeloid Leukaemia NCT01460693; SPIRIT2; 4443; 2007-006185-15; ISRCTN54923521.	N = 810 Estimated completion date: August 2017.
SPIRIT 3: To evaluate the most effective way to use imatinib, nilotinib and ponatinib in the treatment of chronic myeloid leukaemia 2012-005696-14; ISRCTN60655195; SPIRIT3; A15810.	N = 1000 Estimated completion date: September 2023.

Relevant services covered by NHS England specialised commissioning

National Programme of Care Group B - Cancer and blood.

Clinical Reference Group B17 - Teenage and Young People Cancer.

Appendix 3 – Implementation submission

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 imatinib and nilotinib prescribed in primary care and in hospitals and dispensed in the community in England between April 2009 and October 2013. These data need to be treated with caution as both medicines have more than one licensed indication. Dasatinib was not recommended in TA251 and so prescribing data has not been presented for this medicine.

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

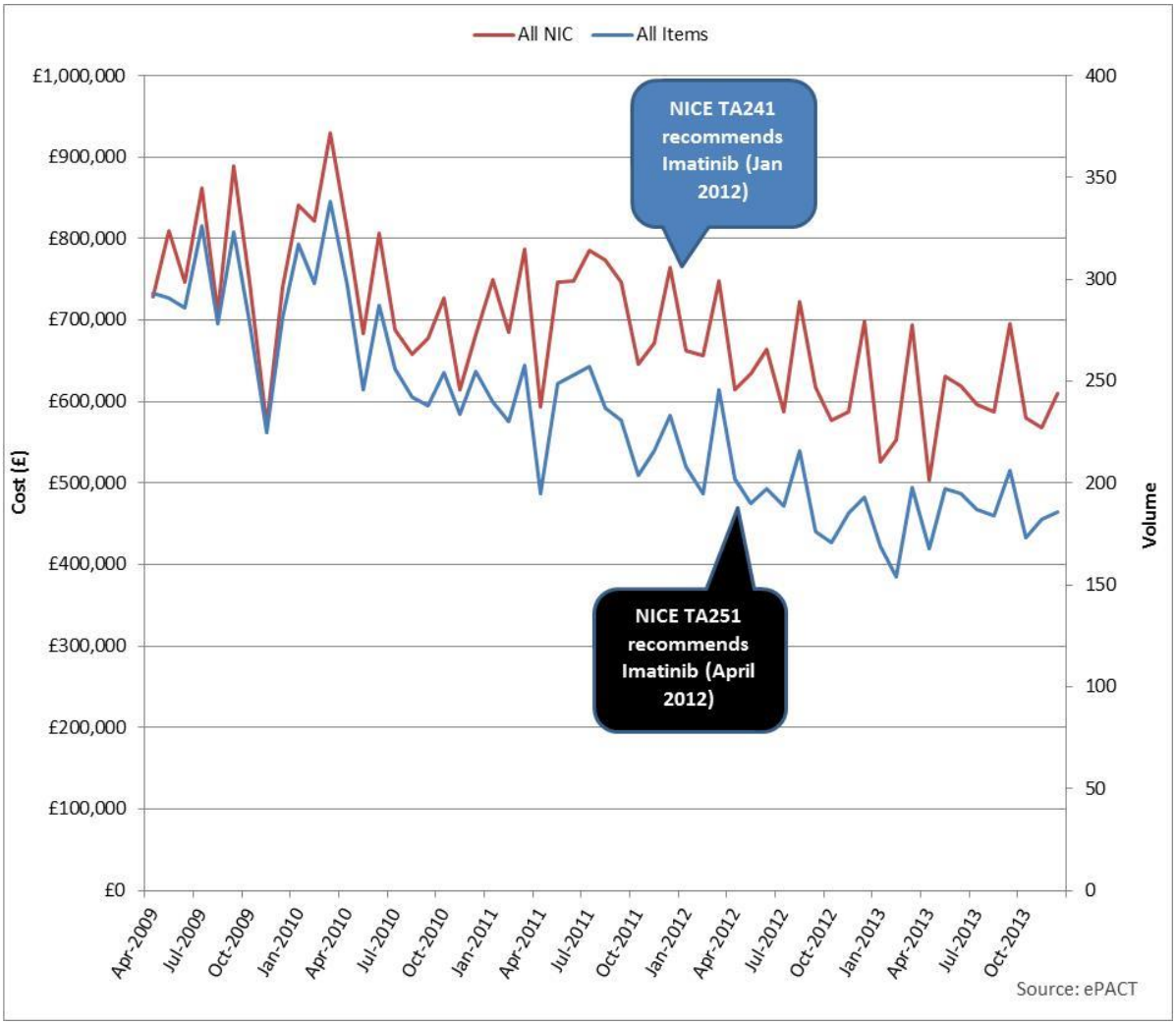
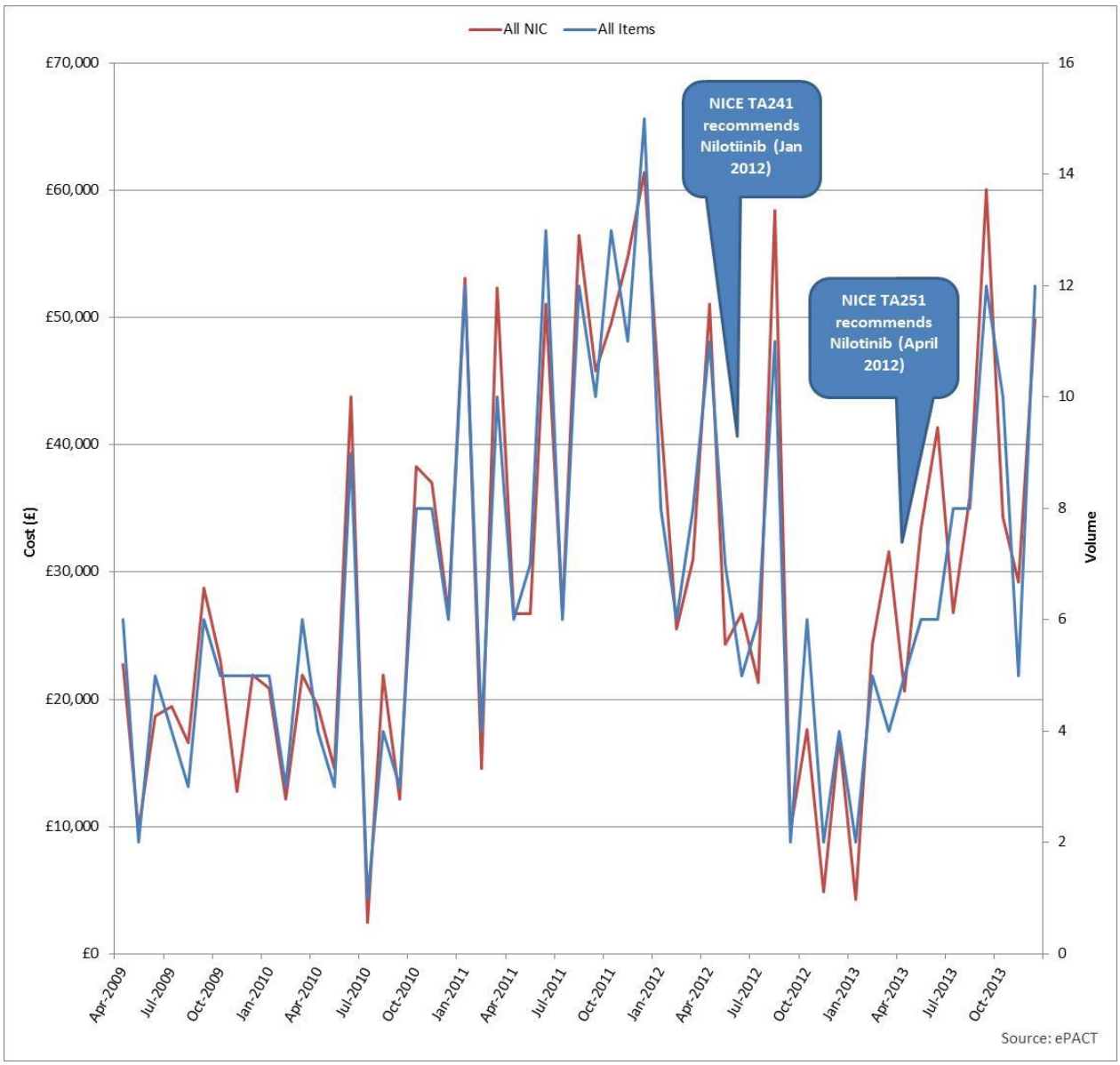


Figure 2 Cost and volume of nilotinib prescribed in primary care and hospitals that have been dispensed in the community in England

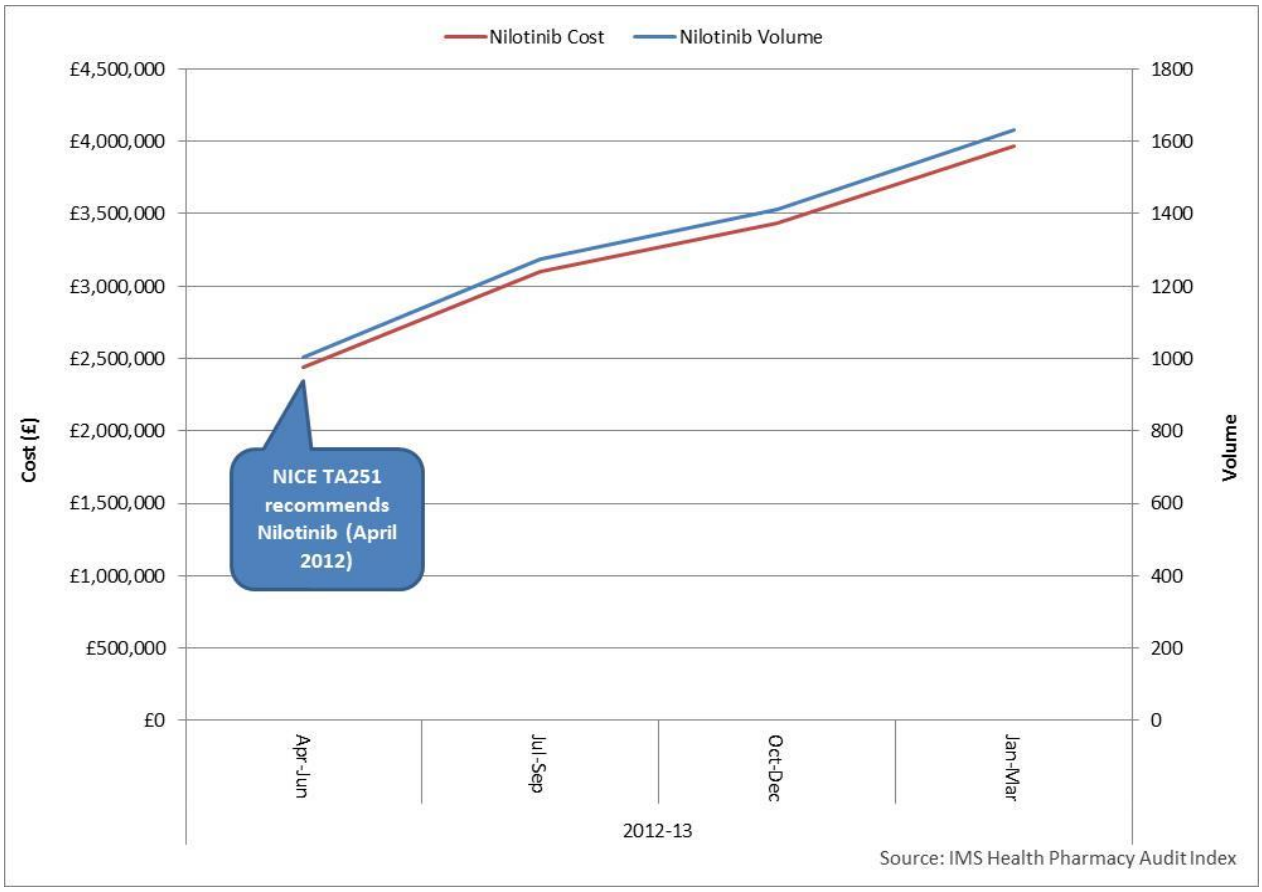


1.2. Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index (HPAI) data on the net ingredient cost (NIC) and volume of imatinib prescribed and dispensed in hospitals in England between April 2008 and March 2013. Data for nilotinib is presented on the same basis for the period covering April 2012 to March 2013. These data need to be treated with caution as these medicines have more than one licensed indication.

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

Figure 4 Cost and volume of nilotinib prescribed in hospitals in England



2. Implementation studies from published literature

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

3. 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.