NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA86; Imatinib for gastrointestinal stromal tumours, and TA209; Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours

This guidance was issued in: TA86 was issued in October 2004; TA209 was issued in November 2010

The review date for this guidance is: TA86 and TA209 August 2013

1. Recommendation

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

2. Original remit(s)

TA86: "To appraise the clinical and cost effectiveness of imatinib in its licensed indication for treatment of gastrointestinal stromal tumours"

TA209: “To appraise the clinical and cost effectiveness of imatinib in its licensed indication for the treatment of gastrointestinal stromal tumours"

3. Current guidance

TA86

1.1 Imatinib treatment at 400 mg/day is recommended as first-line management of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic gastro-intestinal stromal tumours (GISTs).

1.2 Continuation with imatinib therapy is recommended only if a response to initial treatment is achieved within 12 weeks.

1.3 Responders should be assessed at intervals of approximately 12 weeks thereafter. Continuation of treatment is recommended at 400 mg/day until the tumour ceases to respond.

1.4 An increase in the dose of imatinib is not recommended for people receiving imatinib who develop progressive disease after initially responding.

~~1.5 For the purpose of this guidance, response to imatinib treatment should be assessed on the basis of the results of diagnostic imaging to assess size and density of the tumour(s), patients’ symptoms and other factors, in accordance with the Southwest Oncology Group (SWOG) criteria detailed in Appendix D.~~

~~For the purpose of this guidance, response to therapy is defined as the SWOG classifications of complete response, partial response or stable disease.~~

[This recommendation has been updated and replaced by NICE technology appraisal guidance 209.]

1.6 The use of imatinib should be supervised by cancer specialists with experience in the management of people with unresectable and/or metastatic GISTs.

TA209

This guidance updates recommendation 1.5 of TA86. All other recommendations in TA86 still stand.

1.1 Imatinib at 600 or 800 mg/day is not recommended for people with unresectable and/or metastatic gastrointestinal stromal tumours whose disease has progressed after treatment with 400 mg/day imatinib.

1.2 People who are currently receiving 600 or 800 mg/day imatinib for unresectable and/or metastatic gastrointestinal stromal tumours should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

4. Rationale[1]

The new evidence on the clinical effectiveness of starting therapy with imatinib at 800 mg/day showed no statistically significant difference in overall survival and the best overall response was nearly identical in the 400 and 800 mg/kg groups. Limited evidence suggests that PET scanning could provide early information on disease response to imatinib, but this is unlikely to affect the recommendations. There is some new evidence that measuring imatinib plasma concentrations to individualise imatinib therapy may optimise long-term outcomes but further studies would be needed to establish an efficient testing programme as well as the cost effectiveness of such a programme. Therefore, the new evidence does not warrant a review of NICE technology appraisal guidance 86 or 209, and we are not aware that studies are ongoing that would change this view in the near future.

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 September 2009 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are

[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

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

No extension to the marketing authorisation has been received for imatinib for the GISTs indication. At the time of TA86 (2004) the list price of 100 mg imatinib was £778.68 per a pack of 60 tablets. At the time of TA209 (2010) the list price was £802.04. In the BNF, edition 65 (2013), the price of imatinib is listed as £862.19.

Technology appraisal 86

In TA86, the Committee did not recommend starting imatinib therapy with doses above 400 mg/day based on interim results from the European Organisation for Research and Treatment of Cancer (EORTC) and the South West Oncology Group (SWOG). The final results of these 2 studies are now published and show no statistically significant difference in overall survival or progression-free survival between starting imatinib treatment with 400 or 800 mg/day in either trial. In a meta-analysis of both trials, however, there was a statistically significant longer progression-free survival by 4.3 months in favour of 800 mg/day imatinib, but the difference was not statistically significant for overall survival.

The Committee considered that there was no robust evidence that continued treatment with 400 mg/day imatinib is effective in patients with progressive disease. No new evidence relevant to this recommendation was identified during this review.

The Committee recommended further research into the effectiveness of positron emission tomography (PET) to assess tumour response. The literature search for this review identified a study that used 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) to evaluate treatment response in GIST patients receiving sunitinib after imatinib failure (Prior et al. 2009). Tumour metabolism was assessed with FDG-PET before and after the first 4 weeks of sunitinib therapy in 23 patients who received 1 to 12 cycles of sunitinib. The study found that progression-free survival was correlated with early FDG-PET metabolic response ($p<0.0001$), and concluded that FDG-PET is useful for early assessment of treatment response.

The Committee recommended further research into the use of mutational analysis to predict individual response to imatinib treatment, but no studies that would address this recommendation were identified during this review.

Technology appraisal 209

In 209, the Committee agreed that there was no robust evidence for the effectiveness of increased doses of imatinib after disease progression on 400 mg/day imatinib, and that the available evidence (uncontrolled observational studies) was associated with uncertainty and bias. The current literature search did not identify new or ongoing randomised controlled trials evaluating imatinib at 600 or 800 mg/day for GIST patients whose disease progressed on or after 400 mg/day imatinib. It identified a relevant systematic review (Hislop et al. 2011), including 4 studies, which were all considered by the Committee during the development of NICE technology appraisal guidance 209.

In TA209, the Committee concluded that there was not sufficient evidence to justify a separate recommendation for patients with exon 9 mutations. The current literature search did not identify new studies in patients with exon 9 mutations.

The Committee had further concluded that, while measuring imatinib plasma concentrations might potentially individualise imatinib therapy and optimise long-term outcomes, it could not base any recommendations on this because of the lack of evidence at the time of the appraisal and because it was not done in routine clinical practice. The current literature search identified a study in which imatinib plasma levels were analysed in 73 patients with unresectable/metastatic GISTs on the first day and after 29 days of treatment, and were found to be correlated with clinical benefit (Demetri et al, 2009). In addition, a long-term prospective study assessed systemic exposure to imatinib at multiple time points by collecting blood samples from 50 patients with GISTs on the first day of treatment, and after 1, 6, and 12 months (Eechoute et al. 2012). After 90 days of treatment, a statistically significant decrease in imatinib systemic exposure of 29.3% compared with baseline was observed ($p<0.01$), and imatinib plasma levels were found to decrease over time, suggesting that future analyses to study the relationship between plasma levels and clinical benefit should be time specific. It is not clear whether imatinib plasma concentrations are routinely monitored in clinical practice

8. Implementation

A submission from Implementation is included in Appendix 3.

The implementation submission provides data across all 6 licensed indications for imatinib. Because of this, it is difficult to single out the uptake of imatinib for the treatment of unresectable and/or metastatic GISTs in clinical practice.

9. Equality issues

During Appraisal Consultation Document consultation for TA209, comments were made that not recommending 600 or 800mg/day imatinib following disease progression with 400mg/day imatinib unfairly discriminates against people with rare diseases. The respective consultees acknowledged that having a rare disease does not constitute one of the protected characteristics in the current equalities legislation or the Human Rights Act and article 14 of the European Convention on Human Rights (ECHR). The Committee took into account the lack of robust clinical evidence for a survival benefit of higher doses of imatinib, specifically for the subgroup of people with an exon 9 mutation. The Committee was also aware that an alternative treatment option is available for this group of people because NICE technology appraisal guidance 179 recommends that patients have the option to receive treatment with sunitinib after disease progression on 400 mg/day imatinib. The Committee was satisfied that its recommendation was consistent with NICE's legislative obligations under the equalities legislation and the requirement for fairness.

GE paper sign off: Elisabeth George, 01 Aug 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 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

Technology appraisals TA179 Issued: September 2009 Sunitinib for the treatment of gastrointestinal stromal tumours. Reviewed January 2012 where a decision was made to transfer the guidance to the static guidance list

Technology appraisals TA179 Sunitinib for the treatment of gastrointestinal stromal tumours Issued: September 2009. Reviewed January 2012 and added to the static list.

Technology appraisals TA196 Imatinib for the adjuvant treatment of gastrointestinal stromal tumours Issued: August 2010 Reviewed December 2012 where it was agreed that a review of TA196 will tbe planned into the technology appraisals work programme.

Details of new products

Drug (manufacturer)	**Details (phase of development, expected launch date,)**
Nilotinib (Novartis Pharmaceuticals UK Ltd)	Currently indicated for the treatment of adult patients with Philadelphia chromosome positive chronic myelogenous leukaemia (CML)

Registered and unpublished trials

Trial name and registration number	**Details**
A Phase 3 Study to Evaluate Efficacy and Safety of Masitinib in Comparison to Imatinib in Patients With Gastro-Intestinal Stromal Tumour in First Line Medical Treatment (NCT00812240)	Estimated Enrolment: 222 This study is currently recruiting participants. Estimated Study Completion Date: December 2013

References

Demetri, G. D., Wang, Y., Wehrle, E., Racine, A., Nikolova, Z., Blanke, C. D., Joensuu, H., and von, Mehren M. (2009) Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors. *Journal of Clinical Oncology*.27 (19) (pp 3141-3147).

Eechoute, K., Fransson, M. N., Reyners, A. K., De Jong, F. A., Sparreboom, A., Van Der Graaf, W. T. A., Friberg, L. E., Schiavon, G., Wiemer, E. A. C., Verweij, J., Loos, W. J., Mathijssen, R. H. J., and De, Giorgi U. (2012) A long-term prospective population pharmacokinetic study on imatinib plasma concentrations in GIST patients. *Clinical Cancer Research*.18 (20) (pp 5780-5787).

Hislop, J., Quayyum, Z., Elders, A., Fraser, C., Jenkinson, D., Mowatt, G., Sharma, P., Vale, L., and Petty, R. (2011) Clinical effectiveness and cost-effectiveness of imatinib dose escalation for the treatment of unresectable and/or metastiatic gastrointestinal stromal tumours that have progressed on treatment at a dose of 400 mg/day: a systematic review and economic evaluation. *Health Technology Assessment* 15 1-171.

Prior, J. O., Montemurro, M., Orcurto, M. V., Michielin, O., Luthi, F., Benhattar, J., Guillou, L., Elsig, V., Stupp, R., Delaloye, A. B., and Leyvraz, S. (2009) Early prediction of response to sunitinib after imatinib failure by 18F-fluorodeoxyglucose positron emission tomography in patients with gastrointestinal stromal tumor. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 27 (3) 439-445.

Appendix 3 – Implementation submission

Review of NICE technology appraisal guidance No. 86 & 209; Imatinib for gastrointestinal stromal tumours (part review) and Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours

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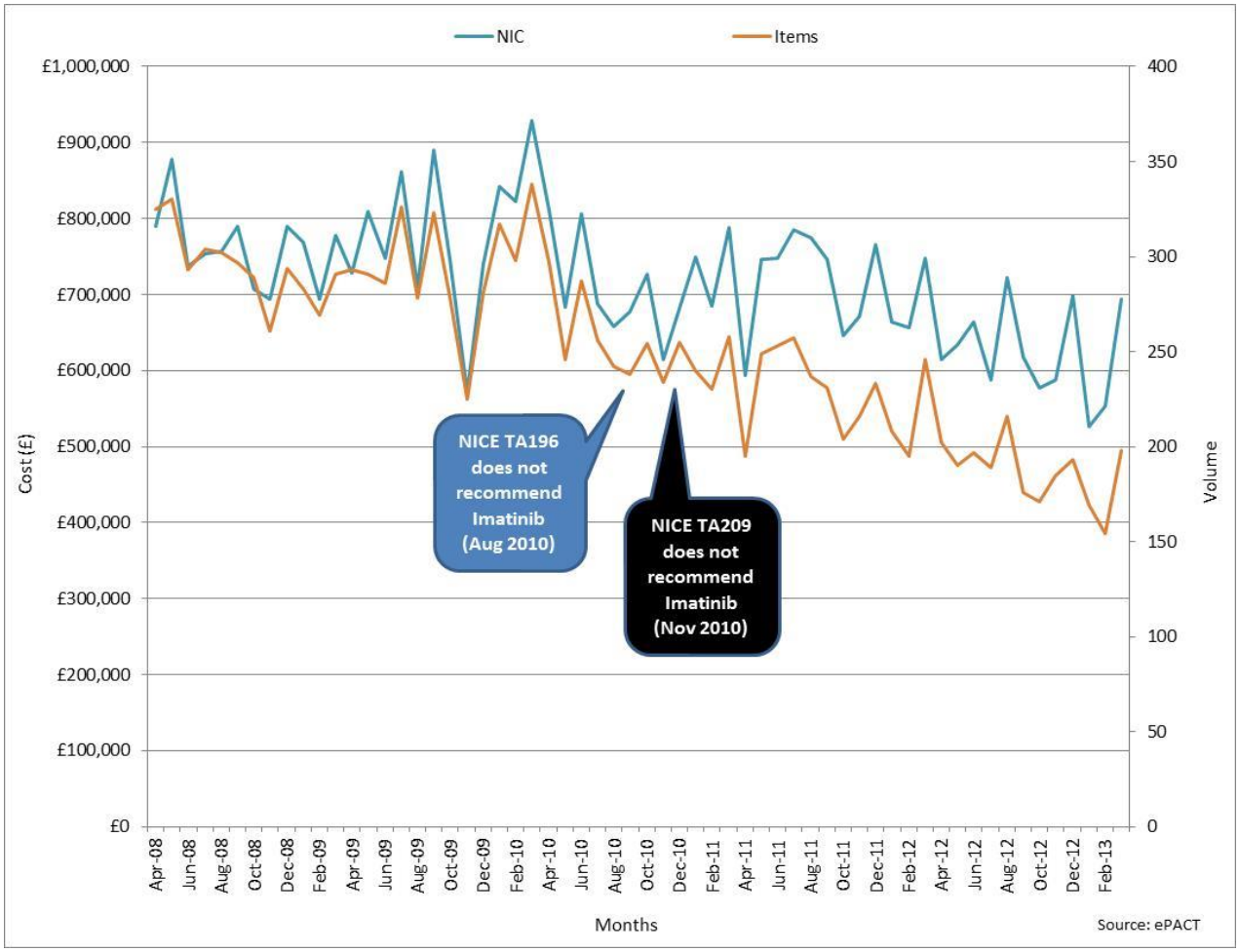
Contents

1. Routine healthcare activity data

1.1. ePACT data

This section presents electronic prescribing analysis and cost tool data on the net ingredient cost (NIC) and volume of Imatinib prescribed in primary care and in hospitals dispensed in the community in England. These data need to be treated with caution as there is more than one indication for Imatinib.

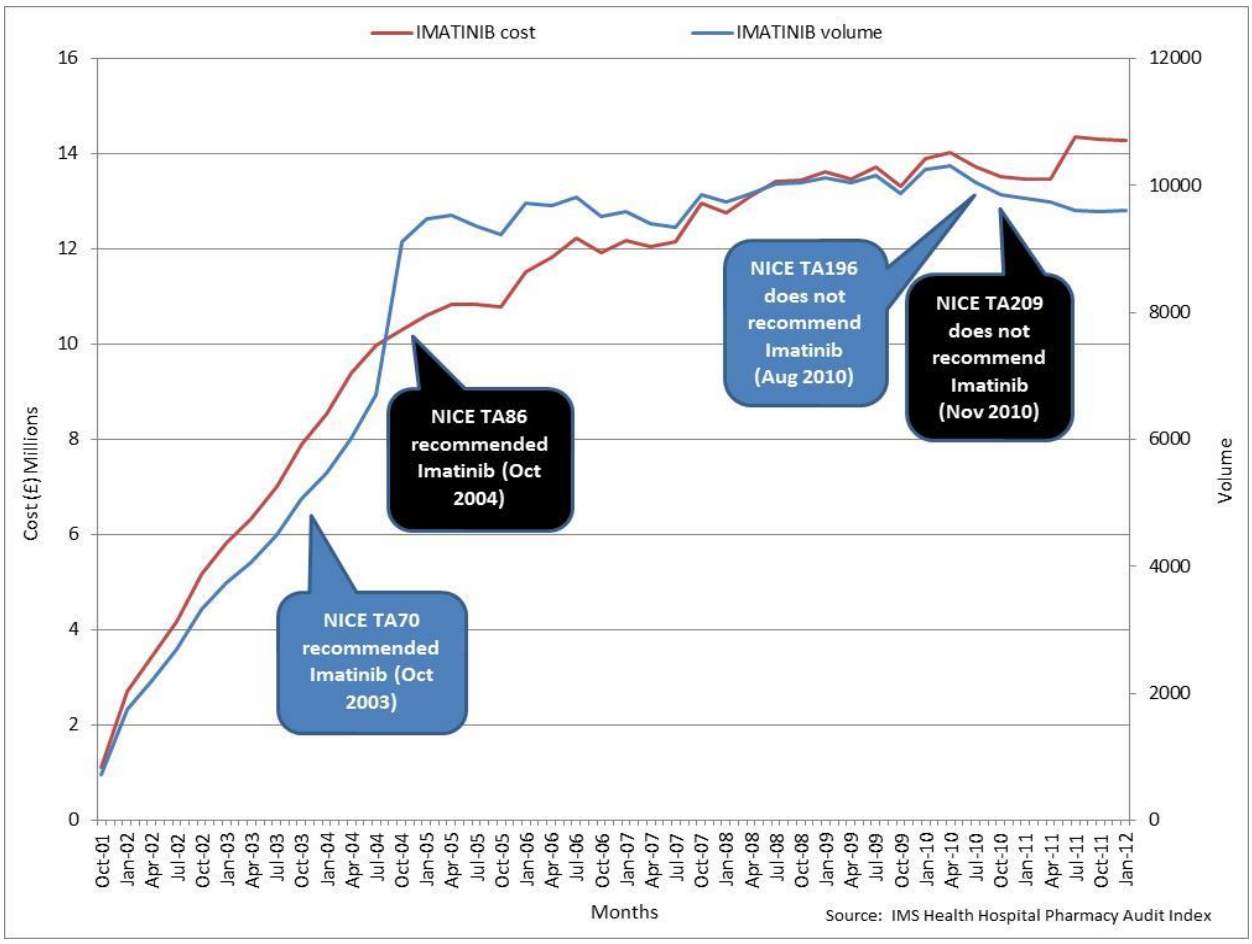
Figure 1 Cost and volume of Imatinib prescribed in primary care and in hospitals dispensed in the community



1.2. Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index data on the net ingredient cost (NIC) and volume of Imatinib prescribed and dispensed for use in hospitals in England between October 2001 and January 2012. These data need to be treated with caution as there is more than one indication for Imatinib.

Figure 2 Cost and volume of Imatinib prescribed and dispensed in hospitals in England



2. Implementation studies from published literature

Information is taken from the uptake database (ERNIE) website.

2.1 Department of Health (2009) Uptake of NICE approved cancer drugs 2007/2008 London: Department of Health

An analysis of prescribing data across cancer networks. Data show a 35% increase in prescribing of imatinib from 2005 to 2007/08 and a 21% reduction in variation across networks (NB data is not linked to diagnosis).

2.2 Richards, M (2010) Extent and causes of international variation in drug usage: A report for the Secretary of State for Health by Professor Sir Mike Richards CBE

This report looks at medicines usage between countries, using IMS Health data. The WHO defined daily dose or the maximum or prescribed daily dose was used to measure usage. Results rank the UK relative to other countries usage and present calculations showing how close or otherwise the UK is to the average use across groups of other countries. It should be noted that countries other than the UK would not be expected to adhere to NICE guidance making comparisons between countries not possible.

2.3 ***Health and Social Care Information Centre (2012) Use of NICE-appraised medicines in the NHS in England - 2010 and 2011, Experimental Statistics***

This is the 3rd report published by the HSCIC on behalf of the DH to look at the variation in use of positively appraised medicines in relation to the expected use as predicted by NICE. In all, 52 medicines in 25 groups, relating to 35 technology appraisals were considered. Out of the 12 groups where a comparison could be made, observed use by the NHS in England was higher than the predicted use for 6 and lower for 6. For one drug group use was lower on one measure, and higher on another.

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.