

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA117; Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy

This guidance was issued in January 2007.

The review date for this guidance was deferred in 2010 until the results of the EVOLVE trial become available.

1. Recommendation

TA117 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 cinacalcet hydrochloride for the treatment of secondary hyperparathyroidism in patients with end stage renal disease on maintenance dialysis therapy.

3. Current guidance

- 1.1 Cinacalcet is not recommended for the routine treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy.
- 1.2 Cinacalcet is recommended for the treatment of refractory secondary hyperparathyroidism in patients with end-stage renal disease (including those with calciphylaxis) only in those:
 - who have 'very uncontrolled' plasma levels of intact parathyroid hormone (defined as greater than 85 pmol/litre [800 pg/ml]) that are refractory to standard therapy, and a normal or high adjusted serum calcium level, and
 - in whom surgical parathyroidectomy is contraindicated, in that the risks of surgery are considered to outweigh the benefits.
- 1.3 Response to treatment should be monitored regularly and treatment should be continued only if a reduction in the plasma levels of intact parathyroid hormone of 30% or more is seen within 4 months of treatment, including dose escalation as appropriate.

4. Rationale¹

The EVOLVE study did not show significant reductions in cardiovascular endpoints relative to placebo. This implies that recommendation 1.1 does not require review at the present time. With regard to the recommendations in 1.2 and 1.3, these were originally based on the Committee being persuaded that in this extreme situation, where patients are at very high risk of adverse events and have poor quality of life, the incremental cost effectiveness ratio was likely to be reduced to the extent that cinacalcet could be considered a cost-effective use of NHS resources. There was no robust data from a randomised controlled trial in this subgroup and this remains the case. Consequently there is no new evidence that would prompt a review of the guidance at this time.

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 October 2009, the date of the previous review searches, 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

Following review of TA117 in December 2009, it was recommended that a review of the guidance should be deferred until the completion of the EVOLVE trial. The results of this trial are now published (Chertow et al., 2012a), along with a report describing baseline characteristics of enrolled patients (Chertow et al., 2012b). The primary composite end point of the trial was time until death or the first non-fatal cardiovascular event (myocardial infarction, hospitalisation for unstable angina, heart failure or a peripheral vascular event). In the cinacalcet group, 48.2% of patients reached the primary end point compared with 49.2% of those in the placebo group. The relative hazard in the cinacalcet group versus the placebo group was 0.93 (95% confidence interval [CI] 0.85 to 1.02; p=0.11), and the relative hazards for the individual components of the composite end point minimally favoured the cinacalcet group. Secondary end points included fracture, and investigators found that there was no advantage for cinacalcet with regard to time to a first clinical fracture (hazard ratio 0.89; 95% CI 0.75 to 1.07; p=0.218). Adverse effects led to drug discontinuation in 18.1% of patients in the cinacalcet group and 13.0% in the placebo group. Rates of serious adverse events were similar in the two groups.

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

Since the original guidance was issued, a new oral formulation of paricalcitol (Zemplar, AbbVie), which is a modified vitamin D analogue, has come to market beside the existing injection form of the drug. Paricalcitol is licensed for the same indication as cinacalcet; that is, for the prevention and treatment of secondary hyperparathyroidism (SHPT) associated with chronic renal failure. The IMPACT SHPT study (Ketteler et al., 2012) is a multicentre, open-label phase 4 study, in which patients were randomised to receive paricalcitol or cinacalcet plus low-dose active vitamin D. Randomisation and analyses were stratified by mode of paricalcitol administration (intravenous [IV] or oral). The primary efficacy end point was the proportion of patients who achieved a mean intact parathyroid hormone (iPTH) value of 150–300 picograms per millilitre (pg/mL) during weeks 21–28 of the study. In the IV stratum, 57.7% of patients in the paricalcitol group compared with 32.7% in the cinacalcet plus low-dose vitamin D group achieved the primary end point ($p=0.016$). The corresponding proportions of patients in the oral stratum were 54.4% and 43.4% in the paricalcitol and cinacalcet plus low-dose vitamin D groups respectively ($p=0.260$). Investigators found overall superiority of paricalcitol over cinacalcet plus low-dose vitamin D (56.0% versus 38.2%; $p=0.010$) in achieving iPTH 150–300 pg/mL during weeks 21–28 in the whole trial population, with lower incidence of hypercalcaemia for paricalcitol than cinacalcet plus low-dose vitamin D. No completed or ongoing randomised controlled trials comparing paricalcitol with cinacalcet have been identified by the literature search for this review.

The ADVANCE trial (Raggi et al., 2011), identified by the literature search, is a randomised, controlled open-label study comparing the effect of cinacalcet plus low-dose active vitamin D with flexible doses of active vitamin D alone on the progression of vascular and cardiac valve calcification in dialysis patients with SHPT. Investigators observed a trend towards slower progression of vascular calcification among patients randomised to the cinacalcet group, though the primary end point did not reach statistical significance.

In summary, the awaited results of the EVOLVE trial did not demonstrate a statistically significant reduction in the risk of cardiovascular events with cinacalcet, and therefore does not suggest that recommendation 1.1 of the guidance requires review. The IMPACT SHPT study might have provided information on the relative effectiveness of paricalcitol and cinacalcet, but given that the evidence is derived from a single open-label study, and investigates biochemical end points rather than clinical end points, the IMPACT SHPT does not provide solid basis to review TA117. Similarly, the ADVANCE trial did not provide robust evidence to support a review of the guidance. The literature search for this review identified other studies for cinacalcet, but these did not address the research questions identified by the Committee (section 6 in the guidance document), nor did they resolve the uncertainty in the evidence base available during the appraisal. In view of that, the new evidence is not likely to lead to a change in the recommendations in the original guidance.

8. Implementation

A submission from Implementation is included in Appendix 3.

The Hospital Pharmacy Audit Index data show a steady increase in the cost and volume of cinacalcet prescribed and dispensed in hospital from January 2005 to October 2008; this reflects a positive clinical experience with the use of cinacalcet. After October 2008, this increasing trend has been interrupted, and the use of cinacalcet reached a relatively stable state thereafter. Such a phenomenon could happen when an external factor (such as the launch of new competitor drugs or new side effects being discovered during practice) affects adoption in clinical practice, but for cinacalcet it is unclear what caused the change. It is important to note that the data provided do not link to diagnosis nor do they rule out off-label prescribing so it would be difficult to establish from the data the extent to which cinacalcet has been used in accordance with TA117.

The Hospital Pharmacy Audit Index data available for this review proposal do not cover data after January 2012, and so do not show the prescribing pattern for cinacalcet after the launch of the oral formulation of paricalcitol and the publication of the results of the EVOLVE trial.

9. Equality issues

No equality issues were raised in the original guidance.

GE paper sign off: Janet Robertson, 4 April 2013

Contributors to this paper:

Information Specialist: Tom Hudson

Technical Lead: Ahmed Elsada

Implementation Analyst: Rebecca Lea

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 [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.	<p>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.</p> <p>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.</p>	No
The guidance should be updated in an on-going clinical guideline.	<p>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.</p> <p>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).</p>	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

Chronic kidney disease: Early identification and management of chronic kidney disease in adults in primary and secondary care. Clinical Guideline [CG73](#). Issued: September 2008. An update of this guidance has been referred to the Institute. Expected publication date: July 2014.

A related NICE [pathway](#) has also been published.

Chronic Kidney Disease. Quality Standard [QS5](#). Issued: March 2011.

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Treatment of secondary hyperparathyroidism in patients with ESRD on maintenance dialysis therapy.	As before.

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
AMG 416 (Amgen)	Phase III trial due to complete in 2015. UK launch plans unknown.
CTAP101 (Cytochroma)	Phase III study due to complete in July 2014. UK launch plans unknown.

Registered and unpublished trials

Trial name and registration number	Details
Cinacalcet, effects on cardiovascular and bone health in chronic kidney disease (CKD)	Standard therapy ± cinacalcet n = 40
ISRCTN81718275; 2006VAS23.	Completed (~2009)

Trial name and registration number	Details
Pediatric Chronic Kidney Disease Safety and Efficacy NCT01277510; 20070208.	Cinacalcet vs. placebo. Participants aged 6-17 years. N = 100 Estimated primary completion date: November 2014. Estimated study completion date: September 2015.
Compare the Efficacy of Cinacalcet vs Traditional Vitamin D for Secondary Hyperparathyroidism (SHPT) Among Subjects Undergoing Hemodialysis NCT01181531; 20090686; PARADIGM.	N = 312 Completed ~October 2012.
Parathyroidectomy vs Cinacalcet in the Treatment of Secondary Hyperparathyroidism Post Renal Transplantation NCT01178450; 01PTHi; 2008-007017-76.	n = 30 Estimated primary completion date: January 2013.
ADVANCE: Study to Evaluate Cinacalcet Plus Low Dose Vitamin D on Vascular Calcification in Subjects With Chronic Kidney Disease Receiving Hemodialysis NCT00379899; 20060111.	Trial of vitamin D ± cinacalcet. n = 360 Completed ~November 2009.
Cinacalcet stUdy for Peritoneal Dialysis Patients In Double Arm on the Lowing Effect OF iPTH Level NCT01101113; CINA-Kor-01.	Trial of vitamin D ± cinacalcet in Korean patients. n = 66 Completed ~June 2012.
20070360 Incident Dialysis NCT00803712; 20070360.	Trial of vitamin D ± cinacalcet. n = 313 Completed ~September 2011.

Trial name and registration number	Details
<p data-bbox="188 262 735 367">Acute Effects of Cinacalcet on Arterial Stiffness and Ventricular Function in Hemodialysis Patients</p> <p data-bbox="188 405 627 439">NCT01250405; CA2009-0008.</p>	<p data-bbox="762 262 1091 295">Cinacalcet vs. placebo.</p> <p data-bbox="762 333 852 367">n = 23</p> <p data-bbox="762 405 1267 472">Estimated primary completion date: February 2013</p> <p data-bbox="762 510 1235 577">Estimated study completion date: February 2015.</p>
<p data-bbox="188 613 692 719">Treatment of Autonomous Hyperparathyroidism in Post Renal Transplant Recipients</p> <p data-bbox="188 757 571 790">NCT00975000; 20062007.</p>	<p data-bbox="762 613 1091 647">Cinacalcet vs. placebo.</p> <p data-bbox="762 685 868 719">n = 100</p> <p data-bbox="762 757 1267 824">Estimated primary completion date: April 2013.</p> <p data-bbox="762 862 1235 929">Estimated study completion date: June 2013.</p>

References

Ketteler M, Martin K, Cozzolino M et al. (2012) Paricalcitol versus cinacalcet plus low-dose vitamin D for the treatment of secondary hyperparathyroidism in patients receiving haemodialysis: study design and baseline characteristics of the IMPACT SHPT study. *Nephrology Dialysis Transplantation* 27 (5): 1942-1949.

Chertow G, Block G et al. (2012a) Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *New England Journal of Medicine* 367 (26): 2482-2494.

Chertow G, Correa-Rotter R, Block G et al. (2012b) Baseline characteristics of subjects enrolled in the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial. *Nephrology Dialysis Transplantation* 27 (7): 2872-2879.

Raggi P, Chertow G, Torres P et al. (2011) The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrology Dialysis Transplantation* 26 (4): 1327-1339.

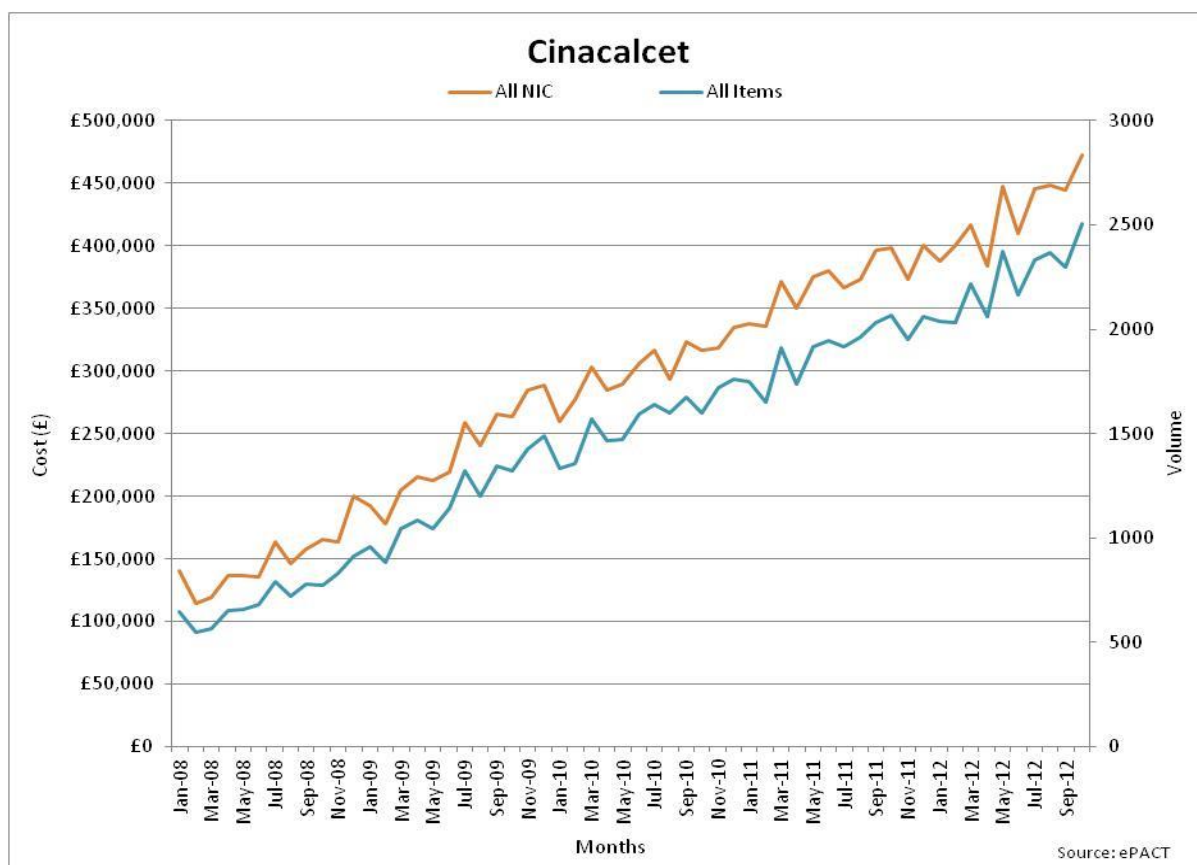
Appendix 3 – Implementation submission

1 Routine healthcare activity data

1.1 ePACT data

This section provides information on the cost and volume of cinacalcet prescribed in primary care and dispensed in the community in England, using data obtained from the electronic Prescribing Analysis and Cost Tool (ePACT) system. Cost and volume data on hospital prescriptions dispensed in the community have also been obtained from hospital ePACT. These data show cost and volume data from January 2008 to October 2012. All costs stated in this report are based on net ingredient cost (NIC).

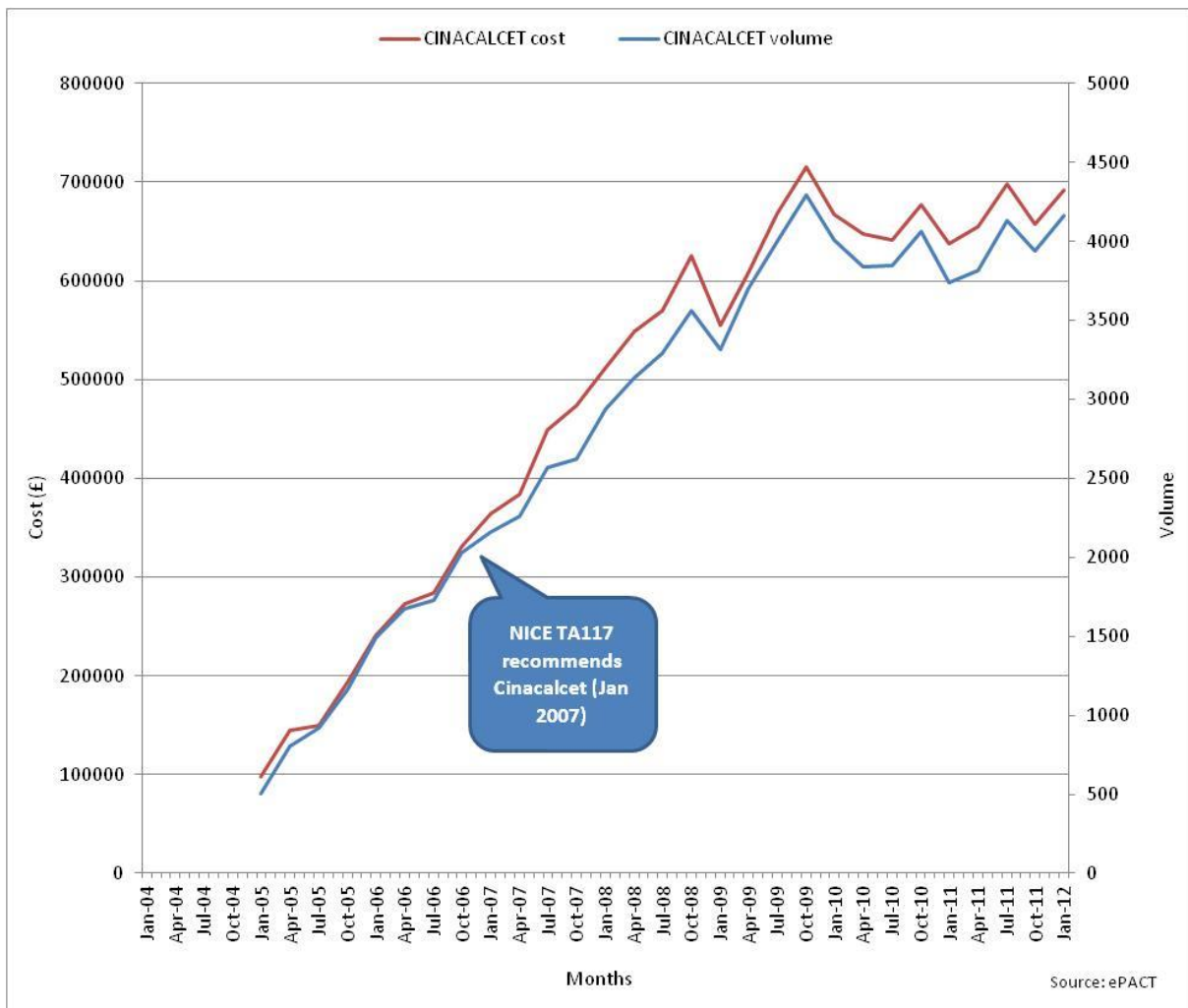
Figure 1 Cost and volume of Cinacalcet prescribed in primary care and in hospitals, dispensed in the community in England



1.2 Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index data on the cost and volume of cinacalcet prescribed and dispensed in hospitals between July 2000 and January 2012. Cost and volume of cinacalcet dispensed in hospitals is shown in Figure 2. All costs stated in this report are based on net ingredient cost (NIC). Unfortunately this data does not link to diagnosis so needs to be treated cautiously in relation to the specific recommendations of the guidance.

Figure 2 Cost and volume of Cinacalcet dispensed in hospitals between July 2000 and January 2012



2 Implementation studies from published literature

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

3 Qualitative input from the field team

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

There were issues with the national costing template for cinacalcet as the national cost was different from the sum of local costs.

Implementation appendix : 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.