Use of NICE appraised medicines in the NHS in England – 2010 and 2011, Experimental statistics
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Author: The Health and Social Care Information Centre, Prescribing and Primary Care Services

Responsible Statistician: David Lloyd, Senior Service Manager

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Executive Summary

This report, “Use of NICE appraised medicines in the NHS in England – 2010 and 2011, Experimental statistics” is the third review of the use by the National Health Service in England of medicines positively appraised by the National Institute for Health and Clinical Excellence.

The 2009 Pharmaceutical Price Regulation Scheme (PPRS)\(^1\), an agreement between the Department of Health (DH) and the Association of the British Pharmaceutical Industry (ABPI), aims to ensure the NHS has access to good quality branded medicines at reasonable prices, and promotes a healthy, competitive pharmaceutical industry. The 2009 PPRS agreement contains a commitment to publish, on an annual basis, metrics for usage by the NHS in England of a number of medicines positively appraised by the National Institute for Health and Clinical Excellence (NICE).

Data on the number of patients diagnosed with specific conditions or being treated is not collected centrally by the NHS and so predicted use (calculated using the estimated number of eligible patients, the average dose and average length of treatment) was compared with observed use. This was not possible for all of the medicines included here, usually due to differences between the total indications for the use of a medicine and the indications appraised by NICE. Such medicines appear in the second part of the results section with an explanation of the difficulties involved in making a valid comparison. Readers are invited to make suggestions to allow analysis of these medicines in future publications.

In most cases data on observed use of the selected medicines was taken from the primary care prescribing data (ePACT), prescriptions issued in secondary care but dispensed in the community (Hospital ePACT) and secondary care data (Hospital Pharmacy Audit Index from IMS Health - HPAI). In some cases data provided by the manufacturer was used.

All medicines positively appraised by NICE were considered for inclusion in this report, though many were subsequently excluded because of significant difficulties with the calculation of predicted or observed use.

In all, 52 medicines in 25 groups, relating to 35 technology appraisals, were considered. Out of the 13 groups where a comparison could be made (these are presented in Section 1 of the technology section results), observed use by the NHS in England was higher than the predicted use for 6 and lower for 6 with one medicine, ranibzumab, where use was higher if measured in milligrams but lower when measured in vials. The results are summarised in the following table as the ratio between expected use and the observed use. A ratio less than one shows that actual use was lower than expected, and a ratio greater than one indicates that actual use was higher than expected. Note that a result greater than one does not mean that all NHS organisations were above the expected value and similarly a value less than one does not mean that all organisations were below. These figures can only be interpreted appropriately by looking at the corresponding sections of the report where the full analysis is

presented. They should also be read in conjunction with the parts of the report explaining the estimation process, data quality and experimental nature of the statistics.

Table 1: Summary of comparisons between expected and observed use of NICE appraised medicines

<table>
<thead>
<tr>
<th>Technology</th>
<th>Result 2010</th>
<th>Result 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temozolomide</td>
<td>1.96</td>
<td>2.05</td>
</tr>
<tr>
<td>Acute Coronary Syndrome (maximum model)</td>
<td>0.93</td>
<td>0.80</td>
</tr>
<tr>
<td>Riluzole</td>
<td>0.65</td>
<td>0.62</td>
</tr>
<tr>
<td>Varenicline</td>
<td>1.27</td>
<td>1.17</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>0.88</td>
<td>0.75</td>
</tr>
<tr>
<td>Ranibizumab (measured in DDDs)</td>
<td>2.59</td>
<td>3.16</td>
</tr>
<tr>
<td>Ranibizumab (measured in vials)</td>
<td>0.56</td>
<td>0.69</td>
</tr>
<tr>
<td>Insulin glargine and detemir</td>
<td>1.15</td>
<td>1.07</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.28</td>
<td>1.28</td>
</tr>
<tr>
<td>Statins</td>
<td>2.31</td>
<td>2.37</td>
</tr>
<tr>
<td>Trastuzumab (indications different in each year)</td>
<td>0.89</td>
<td>0.86</td>
</tr>
<tr>
<td>Carmustine implants</td>
<td>1.10</td>
<td>1.26</td>
</tr>
<tr>
<td>Prucalopride</td>
<td>Not applicable</td>
<td>0.11</td>
</tr>
<tr>
<td>Febuxostat</td>
<td>0.03</td>
<td>0.10</td>
</tr>
</tbody>
</table>

For the 11 groups where a valid comparison could not be made (these are presented in Section 2 of the technology results), the reasons why the comparison could not be made are presented along with a series of questions inviting the reader to suggest improvements to the method or data. A further section is included this year exploring an approach to assessing the use of medicines in the treatment of rheumatoid arthritis.

NICE technology appraisals generally recommend use as an option for the treatment of a disease or condition. This means that the technology should be available for a patient who meets the clinical criteria set out in the guidance, subject to the clinical judgement of the treating clinician. The choice to use the technology should only occur when the clinician concludes and the patient agrees that the recommended technology is the most appropriate to use, based on a discussion of all available treatments.

In interpreting these figures it is important to note that predicted and observed use may differ for a variety of reasons and they should not be assumed to definitely indicate either ‘under’ or ‘over’ prescribing. Clinical judgement, the time taken for the population to present to services to enable changes in prescribing, and demographic differences across healthcare economies are potential explanations for variation in results. Also, assumptions about the average length of treatment are central to producing predictions of use and there are difficulties in producing robust estimates of expected numbers of patients at a sub-national level. Further work is necessary to develop these.

This report is classified as an experimental publication. Work continues to improve data collection and estimation methods. Feedback is requested from users to help inform how best to estimate uptake to allow meaningful interpretation of any variation across NHS organisations in future.
Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS), an agreement between the Department of Health (DH) and the Association of the British Pharmaceutical Industry (ABPI), aims to ensure the NHS has access to good quality branded medicines at reasonable prices, and promotes a healthy, competitive pharmaceutical industry. The 2009 PPRS agreement contains a commitment to publish, on an annual basis, metrics for usage by the NHS in England of a number of medicines positively appraised by the National Institute for Health and Clinical Excellence (NICE).

Comparative information enables assessment of the quality, equity of access and efficiency of healthcare services. Effective use of benchmarking can help to identify variation in usage. The Department of Health and Industry are both committed to increasing access to innovative cost-effective medicines in the NHS. To this end:

- The Department of Health has committed to the annual publication of strategic health authority (SHA), primary care trust (PCT) and cancer network-level metrics (whichever is most appropriate for a given medicine) for the uptake of medicines positively appraised by NICE.
- The pharmaceutical industry has committed to supporting this initiative through sharing of appropriate datasets on medicines usage.
- The metrics will be published through suitable channels on an on-going basis.

This experimental report is the third publication of annual data on the use of NICE appraised medicines in the NHS in England. It is published by the NHS Health and Social Care Information Centre (HSCIC) on behalf of the Department of Health.

Metrics Expert Group and Metrics Oversight Group

Following a review of the arrangements for developing the pharmaceutical metrics, two new groups were established to deliver this work. In September 2011 the Metrics Working Group was replaced by the Metrics Expert Group (MEG). MEG is now responsible for the technical development of the metrics and a new Metrics Oversight Group (MOG) was established to provide strategic leadership and direction to this work.

MEG is chaired by a DH Statistician, and the membership is comprised of representatives from DH, the ABPI, HSCIC, NICE, the Office of Health Economics (OHE) and representatives from individual pharmaceutical companies: MSD, Novartis, Roche and Sanofi. MEG reports to the MOG.

MOG is jointly chaired by the Head of Profession for Statistics, (HSCIC) and an ABPI Board of Management member (Managing Director of Sanofi). The MOG membership is comprised of representatives from DH (including the chair of MEG), the ABPI (including an ABPI member company), NICE, HSCIC and the NHS.

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The first report was published in September 2009.\(^3\) It considered 26 medicines positively appraised by NICE, covering 13 technology appraisals. Out of the 12 appraisals where a comparison could be made, observed use by the NHS in England was higher than the predicted use for seven and lower for five.

The second report was published in January 2011\(^4\). It considered 47 medicines in 18 groups, relating to 29 technology appraisals. 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 eight and lower for three.

This report considers 52 medicines covering 35 technology appraisals (TA). It compares actual usage data with an estimate of the eligible population for NICE recommended medicines within the NHS in England where possible and shows variation between organisations. Section 1 comprises those medicines where a direct comparison between observed and estimated uptake of a medicine is possible. Section 2 of this report contains a selection of medicines where a direct comparison is not possible, or where greater uncertainty exists in the parameters or assumptions used to generate the estimate. Inclusion of a medicine in section 2 does not infer that it is of lesser significance than those included in section 1, it is purely to illustrate the methodological challenges involved in this work. These medicines are illustrative examples rather than the complete list of those medicines not included in section 1.

This year we include a third section on the use of anti-TNF and related medicines for the treatment of rheumatoid arthritis. This work was largely done by industry members of MEG with support from companies and NICE.

The previous publications made a number of recommendations for the further development of the metrics:

- Increased collaboration with the pharmaceutical industry and homecare companies
- Further development of the methodology for deriving estimates of eligible patients:
  - particularly where a medicine is recommended as an option among a number of treatments
  - at sub national level
  - through collaboration with clinical and other networks
- Continue to explore how best to include drugs with multiple indications:
  - the use of medicines by diagnosis, where guidance does not cover all indications
  - where multiple drugs are licensed for an indication, but the drugs have additional indications that differ

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- where different indications require different doses and duration of treatment

Progress has been made on a number of these issues as part of the development of this report, however further work is needed. This is discussed in the ‘Future Developments’ section of this report.

**Experimental Status**

This information is released under ‘experimental' status. This is a concept used for statistics in certain defined circumstances, largely to develop (with user input) new datasets which already have considerable immediate value to users, but are not fully developed and do not yet meet the quality standards of National Statistics. It is important that users understand that cautions apply to the interpretation of this data. More details are given within the report.

**Feedback**

There is an expectation that these metrics are developed further, taking account of informed feedback from users. Feedback from the previous report has been considered in the drafting of this document. Please use the associated feedback form, which includes questions and requests, general comments and suggestions.
Industry engagement

In February and April 2011, the ABPI held industry meetings with key stakeholder companies in order to suggest improvements in the data validation process and improve provision of data for the report. Industry colleagues identified a need to facilitate industry communications, to identify appropriate stakeholders within industry to engage with this work at an early stage and to ensure better understanding of the report's findings.

Following this early engagement, the ABPI was able to identify key contacts in stakeholder companies. It was agreed that they would act as key ABPI contacts on the report within their organisations. This ensured that companies understood the significance of their input in validating the NICE estimated eligible population for their medicines and the data validation process.

Due to particular complexities with biologic medicines and their significance for the NHS, an industry specific group was established to focus on the anti-TNF and other biologic medicines used for rheumatoid arthritis.

This group of medicines had been excluded from previous reports due to

- methodological and data complexity stemming from these drugs having multiple indications and being an option among others for treatment
- significant volumes being supplied via homecare distribution channels which are not included in the routinely available utilisation data.

Details of the analysis resulting from these discussions appear after Section 2.

Another disease area that required significant manufacturer input was cancer. Engagement with industry assisted in the alignment of manufacturer’s usage data supplied at the Cancer Network level. There are a range of distribution channels available to hospitals within England to purchase products, including via services outside of the hospital pharmacy. For cancer medicines these include compounding companies and homecare service providers.

Manufacturer data on cancer medicines was used as the manufacturers generally possess more complete information on all distribution channels for their own medicines. To ensure the same geographical structures were used by different manufacturers, work was undertaken to ensure alignment of “bricks” (the lowest geographic level at which the data is collected on a commercial basis) and hospitals with cancer networks.

A total of 30 companies engaged directly on the report; these were: Abbott, Amgen, Archimedes, AstraZeneca, Basilea, Bayer, Biogen, Boehringer Ingelheim, BMS, Celgene, Chiesi, Diiachi Sankyo, Eisai, GSK, Janssen Cilag, Lilly, Lundbeck, Menarini, MSD, Merck Serono, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Servier, Shire, Takeda, UCB and Warner Chilcott. However, not all of them have medicines included within the final report due to data or methodological issues.

The companies supporting the work on biologic medicines for rheumatoid arthritis in the industry specific group were: Abbott, BMS, MSD, Pfizer, Roche, and UCB.
Method

The aim of this report is to compare the actual usage of medicines between organisations and against an estimate of the eligible population, where available, during 2010 and 2011. This section of the report describes the methods used to develop the estimates and collate data on usage of medicines.

The main steps taken to develop the comparators are shown in Figure 1 below. Details for each step are contained in the following pages.

**Figure 1: Overview of methodology**

```plaintext
Method selection

Development of estimate of eligible patient population

Opportunity for manufacturer to provide information

Estimate of eligible population finalised

Validation of actual usage - opportunity for manufacturer to provide data

Actual usage figures finalised

Methodology selection

Comparison of actual usage against expected estimated usage of respective medicine(s)
```
Medicine Selection

The starting point for medicines selection was the entire catalogue of NICE appraisals. The MEG group agreed a series of selection and exclusion criteria which would provide an initial list of medicines to be considered for inclusion in the report.

It was agreed with MOG that medicines should be excluded if:

- They did not have a positive appraisal from NICE, or were only recommended for use in research
- They are used primarily to treat children (as usage data are not available by age)
- They are formulated as cream/ointment/foam or gels where dosing could vary significantly from patient to patient.

TAs for devices and non-drug technologies were excluded as they are beyond the scope of this report.

All medicines which had been both included and excluded from the previous reports were reviewed using these criteria. Factors likely to influence whether a drug should be included in the report or not (such as medicines where multiple appraised and non-appraised alternative medicines are available) had been noted from previous reports. These factors, along with discussion around data availability, were used to categorise the remaining medicines to determine their likelihood of inclusion in the report.

At the end of these discussions, a list of medicines was proposed for inclusion.

During the course of the analysis, medicines initially considered for inclusion had to be excluded from the report. This was typically because:

- The medicine had multiple non-appraised indications and it was not possible to separate out usage by indication if data was not available to isolate usage across indications.
- The medicine was recommended as a treatment option amongst several other recommended options, and no data exists to separate out the proportional usage of each option by indication. An example of this would be anti-thrombolytics, where several medicines are NICE appraised for the same indications, leaving treatment options to clinical/patient decision making.
- Dosages, the choice of treatment and treatment length can vary according to tolerance and patient and/or clinician choice (as in epilepsy and the antipsychotic medicines).

These medicines are listed in Appendix A showing the principal reason for exclusion.

Note on report Sections

The report is divided into two main sections. Section 1 is comprised of those medicines where a direct comparison between observed and estimated uptake of a medicine is possible. Section 2 of this report contains medicines where a direct comparison is not
possible, or where greater uncertainty exists in the parameters or assumptions used to generate the estimate. Section 2 is purely to illustrate the methodological challenges some medicines represent. These medicines are examples rather than the complete list of those medicines which could not be included in section 1. This approach also maintains the focus on the experimental statistics in section 1. In addition, a separate section describes an experimental methodology developed to compare the use of medicines for rheumatoid arthritis with an agreed estimate of their usage.

It should be noted that whichever section of the report a medicine features in, there remain uncertainties about uptake stemming from a number of factors. These include, but are not limited to; dosing variation, patient choice, clinician choice and valid alternative options, including non drug interventions.

**Estimates of the eligible patient population**

Data on numerous variables is required to refine population numbers for the particular indications and circumstances where a given medicine is recommended by NICE. Examples of such data include epidemiological parameters such as overall disease prevalence; the proportion of patients within a particular stage of a disease and their previous treatment history. In some cases further detail is needed, for example, the proportion of patients likely to discontinue treatment or choose alternative treatments.

It is not anticipated that the estimated number of patients will be treated, or volume of medicine used, immediately following publication of guidance. It may, for example, be a period of time before patients present for treatment and this level is reached.

Estimates of the eligible patient population can be derived from several sources, including from NICE costing templates for the selected TAs.

**NICE costing templates**

NICE provides costing tools to support the implementation of most technology appraisal guidance published since January 2005. Costing templates are intended for financial planning purposes and provide users with the ability to estimate the local cost impact of implementing guidance at the time of publication. They are a tool to aid implementation and therefore the figures generated by their application should be considered as estimates only and should not be interpreted as NICE guidance in terms of desirable or maximum/minimum figures.

Costing templates contain assumptions based on literature, data sources, clinical opinion and other information. NICE encourages users of the costing templates to modify these assumptions to more accurately reflect local circumstances. However, for the purposes of this report the basic template is modified with up to date data and information. This parameterisation is used to generate the national estimate, and it is assumed that this new information is also representative of uptake at the sub national level. Local practice or circumstances may differ from the assumptions used to create the national estimates and could be a reason for variation.
The assumptions used to produce the costing templates are based on a variety of sources, including:

- Background documents to the guidance
- Previous uptake of similar drugs or technologies
- Experts advising the committees producing the guidance
- Data on co-morbid conditions which might preclude patients from treatment. Where no specific data exists then NICE apply estimates of conditions in the whole population to the subgroup
- Areas that have already implemented the recommended practice ahead of the guidance being issued

In the case of medicines with multiple indications, those indications that had been appraised by NICE were identified. For each indication the process for developing the estimate of the eligible population corresponded to the process for medicines with single indications. Once all the estimates for the NICE appraised indications had been determined, the estimates were combined. In some cases medicines are licensed and used for indications which have not been appraised by NICE. In these circumstances the estimates of eligible populations include only the patients who would be treated for the indications appraised by NICE. In these circumstances it may appear that there is over-use of the medicine, even if this is not the case.

**Manufacturer input to NICE estimates**

Once a draft estimate had been developed, NICE provided the manufacturer with a copy along with a template to provide comments and feedback on the estimate, the calculations and assumptions used, and the reference material used to parameterise it. Company feedback was then critically appraised and where appropriate, NICE updated the draft estimate in accordance with evidence provided by the company.

In some instances it was not possible to generate a complete draft estimate owing to lack of data or a lack of evidence to support necessary assumptions in parameterisation. In these circumstances, as with the draft estimates, the pharmaceutical manufacturers were able to comment and share relevant information to enable an estimate to be developed. This information was critically appraised to assess its potential incorporation. The information was required to be robust, publicly available and verifiable. The majority of amendments suggested by manufacturers were utilised in the final estimates.

**Estimate development in the absence of a costing template**

For some medicines in this report, a costing template was not developed at the same time as the guidance (e.g. where the medicine(s) was appraised prior to costing templates being developed by NICE). In these circumstances an estimate was constructed using a stepwise process similar to that used to develop costing templates. The process involved:

1) A review of the available literature on the epidemiology of the indication(s) for the medicine. Example sources of evidence would be: peer reviewed literature, annual
In other cases, the estimates of the eligible population required updating due to the age of the technology appraisal. For instance, revising an estimate where population data or audit results may have been superseded by new information. Any new information included in the estimates was of the same, or greater quality, than that used in the original estimate, i.e. assumptions based on clinical opinion could potentially be updated with peer reviewed research papers but not vice versa.

All information used to build an estimate of the eligible patient population is that which was available in the year to which the estimate relates. It would not be appropriate to calculate prevalence in 2010 based on 2012 data or publications, for example.

**Populations**

Once estimates of the eligible patient populations had been developed and agreed, the total expected volume of medicine was calculated. This was done using Defined Daily Doses (DDDs) as defined by the World Health Organisation (WHO). In certain circumstances DDDs were not available and average doses were agreed with experts and manufacturers.

In order to apply the total expected volume of medicine to sub-national units (e.g. PCTs or SHAs), it was necessary to calculate a proportional split of the total expected volume across these units. This has been done using prevalence, incidence and population size data.

Where appropriate, Quality and Outcome Framework (QOF) prevalence or incidence data has been used in this calculation at the SHA and PCT level. The report used prevalence data for the 24 months March 2009 to April 2011 (http://www.ic.nhs.uk/statistics-and-data-collections/supporting-information/audits-and-performance/the-quality-and-outcomes-framework/)

Where QOF prevalence or incidence rates were not available, SHA population figures were calculated using GP List Populations of Primary Care Organisations (aggregated to SHAs), extracted from the ADS2010/11 (from: http://www.ic.nhs.uk/pubs/gpregpop10) and reconciled to ONS mid 2009/10 estimates for local authorities (minus special populations).

This process has also been used to produce figures at PCT level. Where a specific subpopulation was identified (e.g. Wet AMD, population over 45 years old), then the assumptions were applied to this subset of the total population.
For cancer medicines, the estimates of the eligible population and usage figures have been applied to Cancer Networks (see Appendix B for details). Cancer Networks bring together the providers of cancer care (organisations that deliver cancer services to patients) and the commissioners of cancer care (organisations that plan, purchase and monitor cancer services) to work together to plan and deliver high quality cancer services for a specific population.

Comparison of expected and observed use

The HSCIC has routine access to data on prescriptions (supplied by the NHS Business Services Authority) and use of medicines in hospitals (supplied by IMNS Health). Usage data was converted to physical quantities and, where appropriate, to Defined Daily Doses to allow comparison with the estimates. In some cases companies advised that the data available to the HSCIC was incomplete and provided their own data after discussion of the completeness of their data collection process.

In some cases adjustments were made where the WHO DDD was not appropriate for the use being considered. Details of such adjustments are given on the relevant sections.
# Data Sources and Limitations

Patients can receive their medicine from the NHS by a variety of routes. The most common is to receive a prescription from their general practitioner (GP) and have it dispensed by a community pharmacy. However there are many other ways detailed in Table 1 below.

## Table 1: routes by which patients can receive medicines from the NHS

<table>
<thead>
<tr>
<th>Route</th>
<th>Method</th>
<th>Data available centrally?</th>
<th>Used in report</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Prescription issued by GP, nurse or other primary care prescriber and dispensed by the practice, a community pharmacy or appliance contractor</td>
<td>Yes (ePACT from Prescription Services)</td>
<td>Yes</td>
</tr>
<tr>
<td>B</td>
<td>Prescription issued by a dentist and dispensed by a community pharmacy (only medicines from a restricted list, mainly antibiotics and toothpaste)</td>
<td>Yes if dispensed in England (List B from Prescription Services)</td>
<td>No</td>
</tr>
<tr>
<td>C</td>
<td>Prescription issued by a hospital prescriber and dispensed by a community pharmacy or appliance contractor</td>
<td>Yes (Hospital ePACT from Prescription Services)</td>
<td>Yes</td>
</tr>
<tr>
<td>D</td>
<td>Prescription issued by a hospital prescriber and dispensed by the hospital pharmacy</td>
<td>Yes if captured by IMS Health HPAI system</td>
<td>Yes</td>
</tr>
<tr>
<td>E</td>
<td>Medicines provided within a hospital (in-patient or out-patient) without a prescription</td>
<td>Yes if captured by IMS Health HPAI system</td>
<td>Yes</td>
</tr>
<tr>
<td>F</td>
<td>Medicine supplied directly by a dentist, general practitioner, pharmacist or nurse (e.g. Walk-in Centre, Out of Hours, Minor Ailment Scheme)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>G</td>
<td>Medicine supplied under a Patient Group Direction</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>H</td>
<td>Medicine supplied to patient via homecare arrangement with a hospital trust</td>
<td>Some is captured in IMS Health HPAI but inconsistently across organisations</td>
<td>Only if in HPAI data or provided by relevant company</td>
</tr>
<tr>
<td>J</td>
<td>Medicines supplied to patients by Mental Health Trusts (no prescription involved)</td>
<td>Only if the data is recorded as part of the IMS Health HPAI</td>
<td>Only if in HPAI data</td>
</tr>
<tr>
<td>K</td>
<td>Medicines supplied (i.e. without a prescription) to prisoners</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>L</td>
<td>Medicines provided in hospices not run by NHS</td>
<td>No unless provided through prescription or from hospital pharmacy which is in IMS Health HPAI system</td>
<td>Only if prescription used or in HPAI data</td>
</tr>
</tbody>
</table>

For this report routes B and F are unlikely to be relevant. Not all Mental Health Trusts use hospital pharmacies and so some of their activity will not be recorded. Similarly not all hospital trusts record their homecare arrangements within their pharmacy systems. It also
needs to be remembered that not all trusts contribute data to the HPAI although the vast majority (about 99 per cent in England) do.

Data from Prescription Services, a division of the NHS Business Services Authority (BSA), (routes A and C) are widely considered to have high levels of accuracy and completeness.

The data collected by IMS Health on issue of medicines from trusts’ pharmacy systems is adjusted by IMS to allow for non-participation in their national figures. Their collection includes trusts covering over 99 per cent of acute hospital beds and so has a high level of participation. Data for lower level geographies are not adjusted and so the SHA data used in the report may be an underestimate because of trusts which do not provide data to IMS Health.

There are known problems with the data in terms of estimating the physical quantity of drug used. In some cases the data collected relating to the use of parenteral formulations does not contain sufficient information to be able to calculate the physical quantity used. In these cases an assumed dose is used. This assumed dose was calculated as the average quantity used per administration.

The issue of supplies via the homecare route which are not recorded in available datasets was identified in last year’s report. Recent discussions between the DH and the homecare companies to secure greater governance and transparency around this service have revealed that this method of supply is used more extensively than previously appreciated and is increasing. The Commercial Medicines Unit of the Department of Health has produced a list of the medicines which are known to be supplied via homecare and estimates their use at £1 billion per annum. This list can be found in the Hospital prescribing report for 2009 available at;


During the process of medicine selection, pharmaceutical companies were invited to comment as to whether homecare was likely to be an issue for their medicines. Where this was the case, they were additionally asked if they were able to provide data which would include homecare use.

This report also uses another source of data. The Prescribing Cost Analysis (PCA) database, held by the Health and Social Care Information Centre, holds national level data on NHS dispensing in England from 1991 onwards. In the charts showing cost over time this source is used as the ePACT systems only hold data for 60 months on a rolling basis.
Data from Companies

Through the ABPI, companies were invited to contribute data where they felt that the data available to the HSCIC was not suitable. Several companies offered to contribute data.

Roche Products Ltd directly offered data to the HSCIC on their products trastuzumab, rituximab, erlotinib, capecitabine, tocilizumab and peginterferon alpha-2a. The company explained how they collected the data and showed comparisons with data collected by IMS Health. The company also provided a statement on the quality of their data which is included in the data quality statement accompanying this publication. The HSCIC agreed to use their data in this report on the basis of this evidence.

Pfizer offered data on sunitinib and etanercept. They gave details of how their data was collected and the HSCIC agreed that their process should produce data which is suitable for use.

MSD offered data on their products peginterferon 2b, infliximab, golimumab and ezetimibe. They gave details of how their data was collected and the HSCIC agreed that their process should produce data suitable for use.

AstraZeneca were able to provide the numbers of patients treated with gefitinib. This data was collected as part of their Patient Access Scheme and relies on trusts claiming the cost of part of the treatment. This acts as a financial incentive to good data collection and so the HSCIC were happy to use it for this purpose.

In addition several companies contributed data on the use of biological medicines for use in rheumatoid arthritis. Details of this work can be found in the section, Biological medicines for Rheumatoid Arthritis.

Other companies also offered data, including: Bayer for rivaroxaba, Boehringer Ingelheim for dabigatran, Janssen (bortezomib) and Astra Zeneca for anastrazole, which we were unable to include in this report for a range of methodological reasons.

We are very grateful to all the companies for their support with this work.
Experimental Status

This report is classified as an Experimental Statistic because of methodological and data problems involved in producing the results. This means that the results cannot be regarded as having the same quality as other statistics published by the Health and Social Care Information Centre.

Ideally this report would give the numbers of eligible patients and report the proportion who were treated in accordance with the relevant TA. Unfortunately the NHS does not routinely record such information in a nationally available form. Instead NICE have constructed estimates of the number of eligible patients and the amount of medicine they would be expected to receive and this report compares the observed use with this figure. The problems in constructing an estimate include:

- Lack of prevalence and incidence data at national level
- Attribution of a national figure to local areas, often based simply on population size
- Multiple indications
- Non appraised indications
- Medicine recommended as an option for treatment

Usage data is limited in its coverage and quality. Problems include:

- Multiple indications for a single drug (usage data gives no information on the problem being treated)
- Cross-boundary flow where a patient from one area is treated in another; this is probably particularly important in the London area and where tertiary centres exist
- When considering differences between areas, the failure of some hospitals to contribute data to the IMS Health data collection
- For drugs used in the treatment of mental health problems, the lack of data collection from some mental health trusts
- Medicines supplied via the homecare route which are not uniformly recorded in pharmacy systems
- Some medicines need to be diluted to the individual patient’s requirements in specialist units; the way these are recorded in the pharmacy systems often does not allow calculation of the actual amount of drug used and sometimes these medicines are not recorded at all by the pharmacy

These problems mean that caution must be exercised in interpreting the figures in the report as providing evidence of under or over-use of the medicines reviewed.
Technologies: presentation of results – Section 1

This section of results includes the following medicines/groups of medicines:

- Temozolomide
- Acute Coronary Syndromes
- Riluzole
- Varenicline
- Naltrexone
- Ranibizumab
- Insulin glargine and insulin detemir
- Osteoporosis
- Statins
- Trastuzumab
- Carmustine implants
- Prucalopride
- Febuxostat

Each technology section is divided into:
  - Summary
  - Estimate of eligible patients
  - Estimated usage (volume)
  - References
  - Observed uptake
  - Results

The summary contains details of the licensed indications and the relevant NICE appraisals for each technology considered. For the complete details of the technology appraisals, please refer to the guidance documents, available on the NICE website (http://www.nice.org.uk/guidance/).

The “Estimate of eligible patients” describes the method by which the number of patients was estimated.

The “Estimated usage (volume)” describes the assumed use of the drug by each eligible patient, where this is possible.

Where estimates are produced using the same model for both 2010 and 2011, the process is shown in detail for 2010 and, for 2011, only the results of the recalculation are shown. In some cases estimates were produced for only 2011. In others, a different model was used for each year. In such cases details are shown for each year.

The “Observed uptake” describes the source of the data and notes any exclusions or special processing involved.

The results are then presented in the form of a ratio between predicted and observed use where possible. A ratio of 0.6 to 1 would indicate that observed use was 40 per cent less than expected while a ratio of 1.4 to 1 would indicate that use was 40 per cent higher than
expected. If a comparison between predicted and observed use can be made the results are always presented at national level with SHA and PCT analyses where possible. If the drug is mainly used for cancer then an analysis by Cancer Network is presented. If small numbers of patients are involved then it may not be possible to present sub-national analyses due to the risk of identification of patients. Only the primary care ePACT system holds PCT level data and so a PCT level analysis is only possible if use of the drug is used predominantly in primary care.

Finally a chart shows the quarterly cost since 2001 or since the drug was introduced if this is later than 2001. Use through the prescription route is shown by data taken from the PCA database which includes all prescriptions dispensed in England (including prescriptions written by dentists and hospital prescribers). The PCA database is used because ePACT data is only available for 60 months. The measure of cost in the PCA data is Net Ingredient Cost which is defined as the basic cost of a drug. It does not take account of discounts, dispensing costs, fees or prescription charges income.

Data for medicine use in hospital is taken from the HPAI database. As explained earlier this may be an underestimate for some drugs because of incomplete recording particularly for medicines supplied via aseptic units or homecare. The measure of cost in the HPAI is the same as in the PCA but this may not be the actual amount paid by hospitals. This is because IMS Health collects the volume of medicines used and then applies the cost using standard price lists. Hospitals sometimes obtain medicines at a discount which will not be reflected in these prices.

It should be noted that a detailed examination of the reasons for variation for individual technologies is beyond the scope of this report. However, in broad terms, variation in the use of medicines between Cancer Networks, SHAs and PCTs may be due to a number of factors including (but not limited to):

- Natural variation in populations, both in demographic profile and disease prevalence
- The national model used for estimation of eligible patients or assumptions of the average length of treatment being inappropriate or inaccurate (for example, due to changes in clinical opinion after the guidance was issued)
- Variation in presentation to the NHS by the relevant populations
- Variation in prescribing choice at the local level
- Variation in the use of alternative products or procedures
- Differences in the extent to which local utilisation information is available
Temozolomide

A: Summary

Temozolomide is licensed for the treatment of newly diagnosed glioblastoma multiforme in adults (in combination with radiotherapy) and subsequently as monotherapy. It is also licensed for second-line treatment of malignant glioma in adults and children over 3 years (BNF 63).

Temozolomide has been appraised by NICE for the treatment of recurrent malignant glioma (NICE technology appraisal guidance 23, 2001):

Patients with recurrent malignant glioma (brain cancer) who have failed first-line chemotherapy treatment with other agents (either because of lack of efficacy or because of side effects) may be considered for treatment with temozolomide. Such patients must have a histologically proven malignant glioma (WHO grades III and IV, or transformed grade II) at first relapse, recurrence or progression (as assessed by imaging), Karnofsky performance status greater than or equal to 70 and a projected life expectancy of 12 weeks or more, at initiation of temozolomide treatment.

Temozolomide is not recommended for first-line chemotherapy treatment for patients with malignant glioma who have failed primary therapy (surgery and/or radiotherapy), except in the context of a randomised controlled trial against a standard-treatment comparator.

Temozolomide and carmustine implants have been appraised separately in NICE technology appraisal guidance 121, 2007.

Temozolomide, within its licensed indications, is recommended as an option for the treatment of newly diagnosed glioblastoma multiforme (GBM) in patients with a World Health Organization (WHO) performance status of 0 or 1.

B: Estimate of eligible patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Estimate</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>51,806,700</td>
<td>(1)</td>
</tr>
<tr>
<td>Mean annual incidence of high-grade glioma per 100,000</td>
<td>3.56</td>
<td>(2)</td>
</tr>
<tr>
<td>Estimated annual number of new cases</td>
<td>1,844</td>
<td></td>
</tr>
<tr>
<td>Proportion of patients with grade IV glioma</td>
<td>1383 (75%)</td>
<td>(3)</td>
</tr>
<tr>
<td>Of those, the proportion who have a WHO status of 0 of 1</td>
<td>692 (50%)</td>
<td>(4)</td>
</tr>
<tr>
<td>Patients who would choose temozolomide (patient or clinical decision)</td>
<td>588 (85%)</td>
<td>(5)</td>
</tr>
<tr>
<td>Recurrent treatment with temozolomide according to TA23</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>738</td>
<td></td>
</tr>
</tbody>
</table>
C: Estimated usage (volume)

Concominant therapy:
Dosage: 75 mg/m² daily for 42 days concomitantly with radiotherapy
Estimated dose per patient 5,513 mg

Monotherapy:
Dosage: 150 mg/m² daily for 5 days, followed by 23 days without treatment, for a maximum of six cycles. The dose may be increased to 200 mg/m² daily in the second and subsequent cycles.
Estimated dose per patient 7,875 mg

Total volume 9.88x10⁶ mg

D: For 2011

Estimate of eligible patients: 743

Estimated usage (volume): 9.94x10⁶ mg

References:


2. Annual incidence data have been taken from: The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma: a systematic review and economic evaluation. (http://www.nice.org.uk/guidance/index.jsp?action=download&r=true&o=34040)

3. The ratio of grade 3 and grade 4 gliomas has estimated using an unpublished regional database covering a population of approximately 2.2 million. The data from this database is consistent with clinical concensus, in that grade 3 gliomas represent about 15% of high grade gliomas and anaplastic oligos (AO) represent about 5% - For the purpose of this report AO gliomas have been grouped together with grade 3 gliomas. Following expert opinion it is assumed that grade 4 (GBM) account for 75% of all gliomas with grade 3 and AO accounting for the rest.

4. Expert opinion: the estimated percentage of patients with a WHO status of 0 or 1 ranged from 40 to 60%; for the purpose of this report a figure of 50% has been used.

5. A small minority of patients may choose not to accept temozolomide, estimated to be 15%, with the other 85% receiving the treatment.
6. Dosage information from the Summary of Product Characteristics (SPC) for Temodal.

7. Average surface area has been taken at 1.75 m². Assuming six cycles of monotherapy at the lower value of 150mg/m², but no dropout.

**Observed uptake**

This medicine is used almost entirely in secondary care and so only HPAI data has been used.

**Results**

The table below shows expected and observed use and the ratio between them for 2010 and 2011. Use in 2010 was 96 per cent more than expected and 105 per cent higher in 2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (mg)</th>
<th>Observed (mg)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>9,880,000</td>
<td>19,344,030</td>
<td>1.96</td>
</tr>
<tr>
<td>2011</td>
<td>9,940,000</td>
<td>20,419,901</td>
<td>2.05</td>
</tr>
</tbody>
</table>

Given the small number of patients, a sub-national analysis is not appropriate.

The chart below shows the net ingredient cost by quarter for England. Data is taken from the IMS Health HPAI system which covers hospital use only.
Acutec Coronary Syndromes (abciximab, eptifibatide and tirofiban)

A: Summary

Abciximab, eptifibatide and tirofiban are recommended for the treatment of acute coronary syndromes.

Abciximab is licensed for the prevention of ischaemic cardiac complications in patients undergoing percutaneous coronary intervention; short-term prevention of myocardial infarction in patients with unstable angina not responding to conventional treatment and who are scheduled for percutaneous coronary intervention (BNF 63).

Eptifibatide is licensed for the prevention of early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction and with last episode of chest pain within 24 hours (BNF 63).

Tirofiban is licensed for the prevention of early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction and with last episode of chest pain within 12 hours (BNF 63).

These medicines have been appraised by NICE for the treatment of acute coronary syndromes (NICE technology appraisal guidance 47, 2002). Some of the recommendations in this appraisal were updated as part NICE Clinical Guideline 94 on unstable angina and NSTEMI.

- Consider intravenous eptifibatide or tirofiban as part of the early management for patients who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3.0 per cent), and who are scheduled to undergo angiography within 96 hours of hospital admission (NICE CG 94).

- Consider abciximab as an adjunct to PCI for patients at intermediate or higher risk of adverse cardiovascular events who are not already receiving a GPI (NICE CG 94).

- It is recommended that a GP IIb/IIIa inhibitor is considered as an adjunct to PCI for all patients with diabetes undergoing elective PCI, and for those patients undergoing complex procedures (for example, multi-vessel PCI, insertion of multiple stents, vein graft PCI or PCI for bifurcation lesions); currently only abciximab is licensed as an adjunct to PCI. In procedurally uncomplicated, elective PCI, where the risk of adverse sequelae is low, use of a GP IIb/IIIa inhibitor is not recommended unless unexpected immediate complications occur (NICE TA47).
B: Estimate of eligible patients

<table>
<thead>
<tr>
<th>Unstable angina and NSTEMI (CG94):</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population aged 35-74</td>
<td>25,038,800 (1)</td>
</tr>
<tr>
<td>Estimated annual incidence people aged 35–74</td>
<td>150,233 (0.60%) (2)</td>
</tr>
<tr>
<td>Population aged 75 and over</td>
<td>4,054,500 (1)</td>
</tr>
<tr>
<td>People with acute coronary syndromes diagnosed each year aged 75 and over</td>
<td>93,254 (2.30%) (2)</td>
</tr>
<tr>
<td>Total acute coronary syndromes (ACS) patients per year</td>
<td>243,486</td>
</tr>
<tr>
<td>Proportion who have ST-segment-elevation myocardial infarction (STEMI)</td>
<td>183,589 (75.40%) (3)</td>
</tr>
<tr>
<td>Predicted proportion with 6-month mortality &gt; 3% (intermediate or higher risk of adverse cardiovascular events)</td>
<td>137,692 (75.00%) (4)</td>
</tr>
</tbody>
</table>

Total estimated patients:

Percentage of ACS population who are of intermediate or higher risk who have a PCI (suitable for abciximab treatment), or have an angiography (suitable for intravenous eptifibatide or tirofiban) | 26,120 (18.97%) (5) |

C: Estimated usage (volume)

There are uncertainties regarding the volumes of individual drugs as the glycoprotein inhibitors are treated as a group within the NICE guidelines. Estimates are therefore presented assuming the minimum dose and the maximum dose to give a lower and upper limit per patient.

**Tirofiban**

By intravenous infusion, initially 400 nanograms/kg/minute for 30 minutes, then 100 nanograms/kg/minute for at least 48 hours (continue during and for 12–24 hours after percutaneous coronary intervention); max. duration of treatment 108 hours

Assuming the minimum duration of 48 hours: 23 mg per patient

Assuming the maximum duration of 108 hours: 51 mg per patient (6)
**Eptifibatide:**
Initially by intravenous injection, 180 micrograms/kg, then by intravenous infusion, 2 micrograms/kg/minute for up to 72 hours, until initiation of coronary artery bypass graft surgery, or until discharge from the hospital (whichever occurs first). Administer up to 96 hours if percutaneous coronary intervention during treatment.

*Assuming the minimum duration of treatment of 24 hours*
235 mg per patient

*Assuming the maximum duration of treatment of 96 hours*
900 mg per patient

**Abciximab:**
Initially by intravenous injection over 1 minute, 250 micrograms/kg, then by intravenous infusion, 125 nanograms/kg/minute (max. 10 micrograms/minute); for prevention of ischaemic complications start 10–60 minutes before percutaneous coronary intervention and continue infusion for 12 hours; for unstable angina start up to 24 hours before possible percutaneous coronary intervention and continue infusion for 12 hours after intervention

*Assuming minimum treatment for ischaemic complications starting 10 minutes before and continuing 12 hrs after intervention.*
26 mg per patient

*Assuming maximum treatment for unstable angina, starting 24hrs before and continuing 12 hrs after intervention.*
40mg per patient

**D: For 2011**

**Total estimated patients:**

26,382 (18.97%)

**References**


2. Calculated incidence from Taylor MJ, Scuffham PA, McCollam PL, Newby DE. 2007. Acute coronary syndromes in Europe: 1 year costs and outcomes. Current Medical Research and Opinion 23(3) 495–503. For people aged 75 and over HES 2007-08 data used (codes I20.0 to I22.9) to calculate incidence.

4. Table 2.6 of NICE CG94. Proportion of patients with greater than 3 per cent chance of death within 6 months equates to a mini-GRACE score of 71 or higher. This includes 75 per cent of the acute coronary syndromes population.

5. Data source: The National Clinical Guideline Centre, Royal College of Physicians. Unstable Angina and NSTEMI: the early management of unstable angina and non-ST-segment elevation myocardial infarction (http://www.nice.org.uk/nicemedia/live/12949/47988/47988.pdf). Percentage was calculated using risk group populations (page 272) and MINAP analysis of acute management strategy by risk group (page 264) for intermediate to high risk groups (groups’ 2a-4).

6. Health Survey for England 2008. Table 3. Average adult weight is 76.9kg.

7. Dosage information from the British National Formulary 63.


Observed uptake

These drugs are used entirely within the secondary sector and so data was taken only from the HPAI database.

Results

The observed use for each drug was converted to an estimated minimum and maximum number of patients. The numbers of patients were then summed and compared with the NICE estimate of the number of eligible patients.

The table below shows expected and observed use and the ratio between them for 2010 and 2011. Use was between 55 per cent and 93 per cent of the expected level for 2010 and between 45 per cent and 80 per cent for 2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (patients)</th>
<th>Observed minimum (patients)</th>
<th>Observed maximum (patients)</th>
<th>Minimum ratio</th>
<th>Maximum ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>26,120</td>
<td>14,262</td>
<td>24,271</td>
<td>0.55</td>
<td>0.93</td>
</tr>
<tr>
<td>2011</td>
<td>26,382</td>
<td>11,864</td>
<td>20,995</td>
<td>0.45</td>
<td>0.80</td>
</tr>
</tbody>
</table>

The charts below compare the observed and expected use for 2010 and 2011 at SHA level.
The chart below shows the net ingredient cost by quarter for England. Data is taken from the IMS Health HPAI system which covers hospital use. A chart of use measured in DDDs follows a similar pattern so the fall from late 2004 onwards reflects a true reduction in use.
Riluzole

A: Summary

Riluzole is licensed to extend life in patients with amyotrophic lateral sclerosis, initiated by specialists experienced in the management of motor neurone disease (BNF 63). Riluzole has been appraised by NICE for the treatment of individuals with the amyotrophic lateral sclerosis (ALS) form of Motor Neurone Disease (MND) (NICE technology appraisal guidance 20, 2001):

Riluzole is recommended for the treatment of individuals with the amyotrophic lateral sclerosis (ALS) form of Motor Neurone Disease (MND).

Riluzole therapy should be initiated by a neurological specialist with expertise in the management of MND. Routine supervision of therapy should be managed by locally agreed shared care protocols undertaken by general practitioners.

B: Estimate of eligible patients

England population 51,806,700 1

UK Prevalence 0.00005 2

Expected patient population 2,590 3

C: Estimated usage (volume)

Daily dose per patient 100 mg 3

Annual daily dose 36500 mg

Total Estimated volume $9.45 \times 10^7$ mg

WHO DDD 100 mg 4

Total DDD $9.45 \times 10^5$

It is not anticipated that the estimated number of patients will be treated, or volume of medicine used, immediately following publication of guidance. It may, for example, be a period of time before patients present for treatment and this level is reached.

The estimated eligible number of patients for this drug is small. Therefore, it is important to consider that the results of the comparative analysis are particularly sensitive to any uncertainties in the estimate. In these cases a small variation in the number of estimated
patients will have a large impact on the ratio to actual usage. Figures pertaining to small treatment populations must be treated with caution.

D: For 2011

Estimate of eligible patients: 2,612

Estimated usage (volume): $9.53 \times 10^5$

References


2. Estimated prevalence is 5-7/100,000 population according to: McDermott CJ, Shaw PJ; Diagnosis and management of motor neurone disease. BMJ. 2008 Mar 22;336(7645):658-62.

3. Dosage information taken from BNF 63

4. WHO DDD is obtained from WHO website: http://www.whocc.no/atc_ddd_index/?code=B01AC04

Observed uptake

These drugs are used within both the primary and secondary sector, so data was taken from both versions of ePACT and from the HPAI database. Secondary care use amounts to 18.8 per cent of the total in 2011 (measured in DDDs).

Results

The table below shows expected and observed use and the ratio between them for 2010 and 2011. Use was 65 per cent of the expected level for 2010 and 62 per cent for 2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (DDDs)</th>
<th>Observed (DDDs)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>945,000</td>
<td>617,880</td>
<td>0.65</td>
</tr>
<tr>
<td>2011</td>
<td>953,000</td>
<td>592,501</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Given the small number of patients, a sub-national analysis is not appropriate.

The chart below shows the net ingredient cost by quarter for England. Data is taken from the PCA database (which covers both primary care and prescriptions issued in hospitals and dispensed in the community) and the IMS Health HPAI system which covers hospital use.
Cost riluzole

- PCA
- Hospital
- Total

TA20 issued January 2001
Varenicline

A: Summary
Varenicline is a selective nicotine receptor partial agonist used as an aid for smoking cessation (BNF 63).

Varenicline has been appraised by NICE as an aid for smoking cessation (NICE technology appraisal guidance 123, 2007):

- **Varenicline is recommended within its licensed indications as an option for smokers who have expressed a desire to quit smoking.**
- **Varenicline should normally be prescribed only as part of a programme of behavioural support.**

B: Estimate of eligible patients

Estimated number of smokers setting a quit date 757,537 (1)

Estimated number of patients treated with:

- Prescription NRT only (66%) 480,278 (2)
- Bupropion (1%) 7,575 (2)
- Varenicline (24%) 204,535 (2)
- No pharmacological treatment 37,877 (2)
- No data reported 30,301 (2)

C: Estimated usage (volume)

Volume pr. 12-week treatment 159.5 mg (3)

Total volume (assuming 1 treatment per patient) 2.89·10^7 mg

WHO DDD 2mg (3)

Total doses based on WHO DDD 1.45x10^7 mg

D: For 2011

**Estimate of eligible patients: 204,757**

**Estimated usage (volume):**
Total volume (assuming 1 treatment per patient): \(3.27 \times 10^7\) mg
Total doses based on WHO DDD: \(1.64 \times 10^7\) mg

References


3. British National Formulary 63: Adult dosage: start 1–2 weeks before target stop date, initially 500 micrograms once daily for 3 days, increased to 500 micrograms twice daily for 4 days, then 1 mg twice daily for 11 weeks (reduce to 500 micrograms twice daily if not tolerated); 12-week course can be repeated in abstinent individuals to reduce risk of relapse.

Observed uptake

This drug is used predominantly within the primary sector and primary care use amounts to over 99 per cent of the total (measured in DDDs). Data was taken from just the primary care version of ePACT.

Results

The table below shows expected and observed use and the ratio between them for 2010 and 2011. The data covers only primary care use and shows that use in the two years was 27 and 17 per cent respectively higher than expected.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (DDD)</th>
<th>Observed (DDD)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>14,450,000</td>
<td>18,291,545</td>
<td>1.27</td>
</tr>
<tr>
<td>2011</td>
<td>16,350,000</td>
<td>19,108,054</td>
<td>1.17</td>
</tr>
</tbody>
</table>

The charts below compare the observed and expected use for 2010 and 2011. The proportion of PCTs with a ratio of greater than one fell from 66.8 per cent in 2010 to 65.6 per cent in 2011.
The chart below shows the growth in the use of varenicline. Data is taken from the PCA database and is shown in cost.
Cost varenicline

Millions


TA123 issued July 2007
Naltrexone

A: Summary

Naltrexone is licensed as an adjunct to prevent relapse in formerly opioid-dependent patients (who have remained opioid-free for at least 7–10 days) (BNF 63).

Naltrexone has been appraised by NICE for management of opioid dependence (NICE technology appraisal guidance 115, 2007):

*Naltrexone is recommended as a treatment option in detoxified formerly opioid-dependent people who are highly motivated to remain in an abstinence programme. Naltrexone should only be administered under adequate supervision to people who have been fully informed of the potential adverse effects of treatment. It should be given as part of a programme of supportive care.*

*The effectiveness of naltrexone in preventing opioid misuse in people being treated should be reviewed regularly. Discontinuation of naltrexone treatment should be considered if there is evidence of such misuse.*

B: Estimate of eligible patients

The number of individuals treated for drug dependence is sourced from the National Drug Treatment Monitoring System. There are difficulties with estimating the number of patients who should be treated with naltrexone due to the NICE recommendation that only highly motivated clients should be treated.

Number of individuals who remained in structured drug treatment programs for 12 weeks or more in England

<table>
<thead>
<tr>
<th>Number of individuals</th>
<th>61,384</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated number of individuals receiving Naltrexone</td>
<td>3.1% (1,902)</td>
<td>2</td>
</tr>
<tr>
<td>Number of individuals who remained in structured drug treatment programs for 12 weeks or more in England</td>
<td>62,077</td>
<td>1</td>
</tr>
<tr>
<td>Estimated proportion of individuals receiving naltrexone</td>
<td>3.1% (1924)</td>
<td>2</td>
</tr>
</tbody>
</table>

C: Estimated usage (volume)

<table>
<thead>
<tr>
<th>Treatment length</th>
<th>6 months</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>1,500 mg/month</td>
<td>4</td>
</tr>
<tr>
<td>Total volume 2010</td>
<td>1.71x10^7 mg</td>
<td></td>
</tr>
<tr>
<td>Total volume 2011</td>
<td>1.73x10^7 mg</td>
<td></td>
</tr>
</tbody>
</table>
WHO DDD 50 mg
Total DDD 2010 3.42x10^5 mg
Total DDD 2011 3.46x10^5 mg

The estimated eligible number of patients for this drug is small. Therefore, it is important to consider that the results of the comparative analysis are particularly sensitive to any uncertainties in the estimate. In these cases a small variation in the number of estimated patients will have a large impact on the ratio to actual usage. Figures pertaining to small treatment populations must be treated with caution.

References


3. NICE technology appraisal guidance TA115. Patients should be treated for an initial period of three months. However extended treatment may be necessary because time to full recovery from opioid dependence is variable. Here we have assumed 6 months treatment on average.

4. NICE technology appraisal guidance TA115. People should receive 25 mg naltrexone on day 1 followed by 50 mg daily thereafter.

5. WHO DDD is obtained from WHO website: http://www.whocc.no/atc_ddd_index/?code=B01AC04

Observed uptake

For the indication appraised by NICE, the appropriate daily dose is 50mg. However low dose versions of naltrexone (typically less than 5mg) are available. In order to match the use to the appraisal, only the 50 mg form has been included.

This drug is used predominantly within primary care. Data was taken from both versions of ePACT and from the HPAI database. Primary care use amounted to 83.8 per cent of the total in 2011 (measured in DDDs).

Results

The table below shows expected and observed use and the ratio between them for 2010 and 2011. This shows that use in the two years was 12 and 25 per cent respectively lower than expected.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (DDDs)</th>
<th>Observed (DDDs)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>342,000</td>
<td>300,734</td>
<td>0.88</td>
</tr>
<tr>
<td>2011</td>
<td>346,000</td>
<td>258,697</td>
<td>0.75</td>
</tr>
</tbody>
</table>
Given the small number of patients a sub-national analysis is not appropriate.

The chart below shows the net ingredient cost by quarter for England. Data is taken from the PCA database (which covers both primary care and prescriptions issued in hospitals and dispensed in the community) and the IMS Health HPAI system which covers hospital use. Note that there was a 40% decrease in the cost of Naltrexone in mid-2007 with further price falls since. This means that the cost trend over time does not indicate usage.
Ranibizumab

A: Summary

Ranibizumab is a vascular endothelial growth factor inhibitor licensed for the treatment of neovascular (wet) age-related macular degeneration given by intravitreal injection by specialists experienced in the management of this condition (BNF 63).

Ranibizumab has been appraised by NICE for the treatment of age-related macular degeneration (NICE technology appraisal guidance 155, 2008):

- Ranibizumab, within its marketing authorisation, is recommended as an option for the treatment of wet age-related macular degeneration if:
  - all of the following circumstances apply in the eye to be treated:
    - the best-corrected visual acuity is between 6/12 and 6/96
    - there is no permanent structural damage to the central fovea
    - the lesion size is less than or equal to 12 disc areas in greatest linear dimension
    - there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)
  - and
    - the cost of ranibizumab beyond 14 injections in the treated eye is met by the manufacturer.

- It is recommended that treatment with ranibizumab should be continued only in people who maintain adequate response to therapy. Criteria for discontinuation should include persistent deterioration in visual acuity and identification of anatomical changes in the retina that indicate inadequate response to therapy. It is recommended that a national protocol specifying criteria for discontinuation is developed.

B: Estimate of eligible patients

England population (43-86 year olds) 22,274,100 (1)
Annual incidence of wet AMD 29,625 (0.13%) (2)

Two eyes affected:
A) Patients presenting with bilateral wet AMD 20,737 (70%) (3)
  - of which, number of patients where one eye is suitable for treatment 18,663 (90%)
  - of which, number of patients where both eyes are suitable for treatment 2,962 (10%)
Number of eyes affected 23,700

One eye affected:
B) Patients presenting with one eye affected: 8,887 (30%) (3)
Additionally, proportion of patients presenting with wet AMD in one 889 (10%) (4)
eye developing wet AMD in their second

Number of eyes affected 9,776

Total number of eyes affected 33,476

**Year one:**

Estimated proportion of eyes meeting NICE criteria for treatment 26,781 (80%) (5)

**Year two:**

Proportion of year 1 patients continuing treatment in year 2 22,764 (85%) (6)

**Total number of eyes, year one and two:** 49,544 (7)

**C: Estimated usage (volume)**

Estimated steady-state (47,528 eyes) reached is reached in year two, based on two year treatment and constant rate of incidence. (7)

Total number of eyes, year one and two: 49,544

Number of injections per year per eye 6 (8)

Total number of injections 297,265

Dose per injection 500 mg (9)

Total volume 1.49x10^8 mg

It is not anticipated that the estimated number of patients will be treated, or volume of medicine used, immediately following publication of guidance. It may, for example, be a period of time before patients present for treatment and this level is reached.

**D: For 2011**

**Estimate of eligible patients:**

Total number of eyes: 50,279

**Estimated usage (volume):**

Total volume 1.50x10^8 mg

**References**

2. The cumulative 15-year incidence rate of wet (exudative) age-related macular degeneration in the Beaver Dam study. Overall incidence was 2.0% which equates,
on average, to 0.133% yearly incidence within the age range (43-86 years). Klein R. Et al. 2007. Fifteen-year cumulative incidence of age-related macular degeneration – The Beaver Dam Eye Study. Ophthalmology, 114:253-262.

3. Source: Costing template accompanying NICE TA155. Clinical experts and consultees estimated that about 70% of patients present with both eyes affected by wet AMD. The majority of patients presenting with bilateral wet AMD would only have one eye that would be suitable for treatment due to disease progression in the fellow eye. A minority of patients (10%) presenting with bilateral wet AMD may be eligible for treatment in both eyes.

4. 8–12% of patients with wet AMD in one eye will develop wet AMD in the second eye every year. In this report the midpoint of 10% has been used. The Macular Photocoagulation Study Group (MPSG) (1997) Risk factors for choroidal neovascularization in the second eye of patients with juxtafoveal or subfoveal choroidal neovascularization secondary to age-related macular degeneration. Archives of Ophthalmology 115:741–7.

5. Source: Costing template accompanying NICE TA155. No data could be identified to allow an estimate to be made on the proportion of patients presenting with wet AMD that fulfil NICE’s criteria for treatment. In the absence of published data, the proportion of patients meeting criteria for treatment is based on expert opinion.

6. It is assumed not all patients receiving treatment in year 1 will continue with treatment in year 2. The MARINA study reported that 90% of patients remained in treatment at 12 months. Anecdotal evidence from discussions with UK clinicians suggests that about 80% of patients continue treatment in year 2. For the purpose of this report a midpoint of 85% has been used. Philip J, Rosenfeld MD, David M et al (2006) Ranibizumab for neovascular age-related macular degeneration. New England Journal of Medicine 355:14.

7. At this time limited data are available to estimate the number of patients presenting in year 1 that will continue treatment in year 3. Additionally, current agreements with the manufacturer states that drug costs for patients requiring more than 14 injections will be met by the manufacturer. Source: Costing template accompanying NICE TA155.

8. The dosing regimen for ranibizumab for the first 2 years is subject to significant uncertainty. Data from the MARINA and ANCHOR trials suggests that patients will receive monthly injections and the NICE guidance estimated that patients would receive 14 injections in the affected eye. The treatment regimen used in this costing template assumes that the affected eye will receive six (three injections in the initial loading phase followed by an additional three) injections in year 1, and five injections in year 2. No data could be identified to estimate the proportion of patients that would continue treatment in year 3.


**Observed uptake**

This drug is used solely within the secondary care sector. Data was therefore taken only from the HPAI database.

**Results**

The standard dose of ranibizumab is 500 micrograms per eye but each vial contains 2,300 micrograms. This drug was included in the report covering 2009 and feedback was received indicating that vials were a better measure than actual volume as the usual procedure would be to use a vial to treat a single patient after which it would be discarded. However it is
known that at least one hospital has applied for and received a manufacturing licence to enable them to re-package any surplus so that it can be used for other patients. The table below therefore shows expected and observed use and the ratio between them for 2010 and 2011 both assuming the total volume was successfully used and also on the assumption that a vial would be used for only one patient. Assuming that the total content of each vial can be used for patient treatment then use in the two years was 159 and 216 per cent respectively higher than expected. If we assume that each vial can only be used to deliver one dose then use was 44 and 31 per cent lower than expected. The true figure lies somewhere between these two estimates.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (0.5 mg doses)</th>
<th>Observed (DDDs)</th>
<th>Ratio</th>
<th>Observed (vials)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>298,000</td>
<td>770,490</td>
<td>2.59</td>
<td>167,498</td>
<td>0.56</td>
</tr>
<tr>
<td>2011</td>
<td>300,000</td>
<td>946,939</td>
<td>3.16</td>
<td>205,856</td>
<td>0.69</td>
</tr>
</tbody>
</table>

The charts below compare the observed and expected use for 2010 and 2011 at SHA level.
The chart below shows the net ingredient cost by quarter for England. Data is taken from the IMS Health HPAI system which covers hospital use.
Insulin Glargine and Insulin Detemir

A: Summary

Insulin glargine and insulin detemir are indicated for the treatment of diabetes mellitus (BNF 63).

Insulin glargine has been appraised by NICE for the treatment of diabetes (NICE technology appraisal 53, 2002). Recommendations in this appraisal relating to type 2 diabetes have been replaced by NICE Clinical Guideline 87 on type 2 diabetes newer agents:

- **Insulin glargine is recommended as a treatment option for people with type 1 diabetes (NICE TA 53)**
- **Initiate insulin therapy from a choice of a number of insulin types and regimens.** Consider, as an alternative, using a long-acting insulin analogue (insulin detemir, insulin glargine) if:
  - The person needs assistance from a carer or healthcare professional to inject insulin, and use of a long-acting insulin analogue (insulin detemir, insulin glargine) would reduce the frequency of injections from twice to once daily, or
  - The person’s lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes, or
  - The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs, or
  - The person cannot use the device to inject NPH insulin (NICE CG 87)
  - Consider switching to a long-acting insulin analogue (insulin detemir, insulin glargine) from NPH insulin in people:
    - who do not reach their target HbA1c because of significant hypoglycaemia, or
    - who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA1c reached, or
    - who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made, or
    - who need help from a carer or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.

B: Estimate of eligible patients

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>England population (17 years or older)</td>
<td>41,464,400</td>
<td></td>
</tr>
<tr>
<td>Diabetes prevalence in England (17 years or older)</td>
<td>2,114,684 (5.10%)</td>
<td></td>
</tr>
<tr>
<td>Proportion of diabetes patients with type 1 diabetes</td>
<td>211,468 (10%)</td>
<td></td>
</tr>
<tr>
<td>(17 years or older)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of diabetes patients with type 2 diabetes</td>
<td>1,903,216 (90%)</td>
<td></td>
</tr>
<tr>
<td>(17 years or older)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes patients in England &lt; 17 years</td>
<td>20,488</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes patients in England &lt; 17 years</td>
<td>328</td>
<td></td>
</tr>
</tbody>
</table>
Total type 1 diabetes patients (all ages) 231,956
Total type 2 diabetes patients (all ages) 1,903,544

**Type 1 diabetes**
patients requiring long-acting insulin (insulin glargine or detemir) 115,978 (50%) (5)

**Type 2 diabetes**
patients requiring long-acting insulin (insulin glargine or detemir) 133,248 (7%) (6)

**C: Estimated usage (volume)**

NICE guidelines do not specify which of the long acting insulins (glargine or detemir) should be used. Therefore only overall dosage can be estimated.

Dosage, assuming treatment 365 days/year:
- for diabetes 1 4.23x10^7 daily doses
- for diabetes 2 4.86x10^7 daily doses
- total 9.10x10^7 daily doses

**D: For 2011**

**Estimate of eligible patients:** 270,271

**References**

5. NICE TA53, section 6.2, assuming all diabetes 1 patients require insulin treatment and subtracting 50% who need basal-bolus regimen.
6. Estimated number of patients requiring long-acting insulin (1st-4th line treatment). Forecast of usage indicated a decrease from 9% to 4% in years 0 and 3, respectively.
We have assumed a midpoint of 7% for the purpose of this report. Source: costing template accompanying NICE CG87.

**Observed uptake**

This drug is used predominantly within the primary care sector and so only data from primary care ePACT was used.

**Results**

The table below shows expected and observed use and the ratio between them for 2010 and 2011. The data covers only primary care use and shows that use in the two years was 15 and 7 per cent respectively higher than expected.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (DDDs)</th>
<th>Observed (DDDs)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>90,967,490</td>
<td>104,229,980</td>
<td>1.15</td>
</tr>
<tr>
<td>2011</td>
<td>98,648,915</td>
<td>105,120,578</td>
<td>1.07</td>
</tr>
</tbody>
</table>

The charts below compare the observed and expected use for 2010 and 2011. The proportion of PCTs with a ratio of greater than one decreased from 72.2 per cent in 2010 to 56.9 per cent in 2011.
The chart below shows the net ingredient cost by quarter for England. Data is taken from the PCA database which covers both primary care and prescriptions issued in hospitals and dispensed in the community.
Prevention of osteoporotic fragility fractures – alendronate, etidronate, risedronate, raloxifene, strontium ranelate, teriparatide and denosumab

A: Summary

Alendronate is licensed for the treatment of postmenopausal osteoporosis; treatment of osteoporosis in men and the prevention and treatment of corticosteroid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy (BNF 63).

Etidronate is licensed for Paget’s disease of bone, treatment of osteoporosis, prevention of bone loss in postmenopausal women and prevention and treatment of corticosteroid-induced osteoporosis (BNF 63).

Risedronate is licensed for Paget’s disease of bone; treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures and prevention of osteoporosis (including corticosteroid-induced osteoporosis) in postmenopausal women (BNF 63).

Raloxifene is licensed for the treatment and prevention of postmenopausal osteoporosis (BNF 63).

Strontium ranelate is licensed for the treatment of postmenopausal osteoporosis (BNF 63).

Teriparatide is licensed for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures; treatment of corticosteroid-induced osteoporosis (BNF 63).

NICE has appraised these drugs for primary prevention of osteoporotic fragility fractures in postmenopausal women (NICE technology appraisal guidance 160, 2008):

- **Alendronate** is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in women with particular risk factors (see guidance).

- **Risedronate and etidronate** are recommended as alternative treatment options for the primary prevention of osteoporotic fragility fractures in postmenopausal women with particular risk factors (see guidance).

- **Strontium ranelate** is recommended as an alternative treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women with particular risk factors (see guidance). NB. This recommendation is currently subject to review.

- **Raloxifene** is not recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women.

NICE has also appraised these drugs for secondary prevention (technology appraisal 161, 2008):
Alendronate is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women with particular risk factors (see guidance).

Risedronate and etidronate are recommended as alternative treatment options for the secondary prevention of osteoporotic fragility fractures in postmenopausal women with particular risk factors (see guidance).

Strontium ranelate and raloxifene are recommended as alternative treatment options for the secondary prevention of osteoporotic fragility fractures in postmenopausal women with particular risk factors (see guidance). NB This recommendation is currently subject to review.

Teriparatide is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women with particular risk factors (see guidance).

At the time of the last report the guidance relating to strontium ranelate was under review. After having examined this additional evidence on strontium ranelate and an independent expert review of the evidence very carefully, the new independent Appraisal Committee reached the same conclusions as the original Appraisal Committee, and so the recommendations on strontium ranelate remain unchanged from those published originally. Consultees then had a chance to appeal against this decision but no appeals were received.

NICE guidance on the use of alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the prevention and treatment of osteoporotic fragility fractures in postmenopausal women therefore remains unchanged.

NICE has also recommended denosumab (TA204) as a treatment option:

For the primary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures:

For patients who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments and

who have a combination of T-score, age and number of independent clinical risk factors for fracture (see section 1.3 of TA 204).

as a treatment option for the secondary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments
As no costing template was produced at the time of TA204 (the cost to the NHS was predicted to be less than £1 million) there is no suitable data to assess the proportion of patients that would receive denosumab versus strontium ranelate where the recommendations for these treatment options overlap.

**B: Estimate of eligible patients**

<table>
<thead>
<tr>
<th>Prevalence of osteoporosis</th>
<th>with no prior fracture</th>
<th>with prior osteoporotic fragility fracture (1, 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women aged 50–54 years</td>
<td>32,584 (2%)</td>
<td>32,584 (2%)</td>
</tr>
<tr>
<td>Women aged 55–59 years</td>
<td>45,546 (3%)</td>
<td>45,546 (3%)</td>
</tr>
<tr>
<td>Women aged 60–64 years</td>
<td>111,125 (7%)</td>
<td>111,125 (7%)</td>
</tr>
<tr>
<td>Women aged 65–69 years</td>
<td>146,172 (12%)</td>
<td>109,629 (9%)</td>
</tr>
<tr>
<td>Women aged 70–74 years</td>
<td>182,410 (17%)</td>
<td>150,220 (14%)</td>
</tr>
<tr>
<td>Women aged 75–79 years</td>
<td>193,284 (21%)</td>
<td>184,080 (20%)</td>
</tr>
<tr>
<td>Women aged 80–84 years</td>
<td>0</td>
<td>190,450 (26%)</td>
</tr>
<tr>
<td>Women aged 80 years or older</td>
<td>425,572 (28%)</td>
<td>0</td>
</tr>
<tr>
<td>Women aged 85 years or older</td>
<td>0</td>
<td>244,094 (31%)</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>1,136,693</strong></td>
<td><strong>1,067,728</strong></td>
</tr>
</tbody>
</table>

Postmenopausal women aged 50 years or older with osteoporosis eligible for treatment

<table>
<thead>
<tr>
<th></th>
<th>(3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>522,878 (46%)</td>
<td>683,345 (64%)</td>
</tr>
</tbody>
</table>
### C: Estimated usage (volume)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Estimated number of women identified and present for treatment (including a reduction due to low adherence rate – see reference 4):</th>
<th>with no prior fracture</th>
<th>with prior osteoporotic fragility fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>212,289</td>
<td>221,031</td>
<td></td>
</tr>
<tr>
<td>Etidronate</td>
<td>4,444</td>
<td>8,541</td>
<td></td>
</tr>
<tr>
<td>Risedronate</td>
<td>40,785</td>
<td>77,559</td>
<td></td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>3,922</td>
<td>15,033</td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>not recommended</td>
<td>11,616</td>
<td></td>
</tr>
<tr>
<td>Teriparatide</td>
<td>0 (0%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

#### Alendronate

- Average length of treatment: Chronic (52 weeks)  
  - Number of doses per week: 1  
  - Total doses (thousands): 11,039  
  - Average dose: 70 mg  
  - Total volume: $7.73 \times 10^8$ mg

#### Etidronate

- Average length of treatment: 90 day cycles  
  - Dosage: 400 mg/day for 14 days, 4 cycles per year  
  - Total volume: $9.96 \times 10^8$ mg

#### Risedronate

- Average length of treatment: Chronic (52 weeks)  
  - Number of doses per week: 1  
  - Total doses (thousands): 2121  
  - Average dose: 35 mg  
  - Total volume: $7.42 \times 10^7$ mg

#### Strontium ranelate

- Average length of treatment: Chronic (52 weeks)  
  - Number of doses per week: 1  
  - Total doses (thousands): 1427  
  - Average dose: 2 g  
  - Total volume: $2.85 \times 10^6$ g
No estimate has been made for the use of teriparatide partly due to its use in homecare and partly due its low use.

It is not anticipated that the estimated number of patients will be treated, or volume of medicine used, immediately following publication of guidance. It may, for example, be a period of time before patients present for treatment and this level is reached.

D. For 2011

**Estimate of eligible patients:**

<table>
<thead>
<tr>
<th></th>
<th>with no prior fracture</th>
<th>with prior osteoporotic fragility fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raloxifene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Average length of treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Number of doses per week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Total doses (thousands)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Average dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Total volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparatide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Average length of treatment</td>
<td>Not licensed for this group</td>
<td>Maximum 18 months</td>
</tr>
<tr>
<td>- Dosage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Total volume</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Estimated number of women identified and present for treatment (including a reduction due to low adherence rate – see reference 4):

- With no prior fracture: 262,590
- With prior osteoporotic fragility fracture: 345,198

**References**

1. Population data from costing templates accompanying NICE technology appraisals TA160 and TA161.

2. Clinical Effectiveness and Cost Effectiveness of Prevention and Treatment of osteoporosis. Produced by the University of Sheffield School of Health and Related Research (ScHARR)


4. The compliance and adherence to bisphosphonate treatments has been documented to be low (Penning-van Beest et al. (2008). Osteoporos Int., 19:511–517). Persistence rate for treatment lasting 7 to 12 months has been shown to range from
37% - 63%. (Kothawala et al. 2007. Mayo clinic Proc, 82:1493-501). An average of 50% has been assumed here, as per costing template accompanying TA160 and TA161.

5. Information from the British National Formulary 63 - Treatment of postmenopausal osteoporosis:

Alendronate: 10mg daily or 70mg once weekly;

Etidronate (Didronel PMO): 90-day cycles, each starting with 400mg/day for 14 days, then calcium carbonate for the remaining 76 days;

Risedronate: 5mg daily or 35 mg once weekly;

Strontium ranelate: 2g once daily

Raloxifene: 60 mg once daily

Teriparatide: One 750 microgram pen provides treatment for 28 days for maximum of 18 months.

**Observed uptake**

Data from both ePACT systems was used for the national analysis. For the PCT level analysis only primary care data was used.

Some preparations of sodium risedronate were excluded as it was clear from the strength that they were intended for treatment of Paget's disease (typical daily dose 30 mg rather than the 5mg normally given for osteoporosis ). Disodium etidronate is also used for Paget's disease and so the analysis excluded the 200 mg tablets and only considered the 400 mg tablets in a combined pack (where these tablets are only used for a small part of the 90 days treatment for which the pack is intended). This also meant devising a new DDD as the WHO figure is 400 mg, reflecting use for Paget's disease. The data were analysed as if the tablets were used over the full 90 days, effectively giving a DDD of 62.2 mg.

For the combined products only the content of the drugs in the guidance was considered, i.e. any additional calcium or vitamin D content was excluded.

Consultations with pharmaceutical companies suggested that data on teriparatide was likely to miss some homecare use. Additionally, the use of the drug is low compared with other osteoporosis drugs. Taking these issues into account, this drug was excluded.

Denosumab was positively appraised by NICE for use by patients who could not tolerate biphosphonates in October 2010 (TA204). Use of this drug has been included in the usage figures for 2011 but not for 2010. The drug is available in two forms, a pre-filled syringe and as a solution for injection. While the solution is more likely to be used for men with bone metastases from solid tumours all primary care usage has been included.

Primary care use of all these medicines amounted to over 99 per cent of total use (measured in DDDs).
Results

The table below shows expected and observed use and the ratio between them for 2010 and 2011. The expected number of DDDs was obtained by taking the number of whole time patient equivalents and multiplying by 365.

Some of these drugs are used for indications not covered by NICE appraisals, e.g. for osteoporosis in men.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected</th>
<th>Observed</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010 (excludes denosumab)</td>
<td>220,135,515</td>
<td>282,688,323</td>
<td>1.28</td>
</tr>
<tr>
<td>2011 (includes denosumab)</td>
<td>221,842,620</td>
<td>284,572,982</td>
<td>1.28</td>
</tr>
</tbody>
</table>

The charts below compare the observed and expected use for 2010 and 2011. The proportion of PCTs with a ratio of greater than one increased from 92.1 per cent in 2010 to 94.0% per cent in 2011. Note that the 2011 usage figures include denosumab but the 2010 figures do not.
The chart below shows the cost of osteoporosis medicines using data from the PCA database. Note that denosumab is included for all time periods and that teriparatide (not included in the analysis earlier) is also included. All forms of sodium risedronate are included so the chart will include some use for Paget’s disease.
The fall in cost from 2006 onwards is due to falls in the price of some products, particularly alendronic acid. The chart below shows the same medicines but measured in Defined Daily Doses.
A: Summary

The statins competitively inhibit an enzyme involved in cholesterol synthesis, especially in the liver. Statins are more effective than other lipid-regulating drugs at lowering LDL-cholesterol concentration but they are less effective than the fibrates in reducing triglyceride concentration. However, statins reduce cardiovascular disease events and total mortality irrespective of the initial cholesterol concentration. (BNF 63)

Statins should be considered for all patients, including the elderly, with symptomatic cardiovascular disease such as those with coronary heart disease (including history of angina or acute myocardial infarction), occlusive arterial disease (including peripheral vascular disease, non-haemorrhagic stroke, or transient ischaemic attacks). (BNF 63)

Statin therapy is indicated for patients older than 40 years with diabetes mellitus (type 1 and 2). In younger patients with diabetes, treatment with a statin is indicated for consideration if there is target-organ damage, poor glycaemic control (HbA1c greater than 9%), low HDL-cholesterol and raised triglyceride concentration, hypertension, or a family history of premature cardiovascular disease. (BNF 63)

Statins are also indicated for the prevention of cardiovascular disease events in asymptomatic individuals who are at increased risk. (BNF 63)

NICE TA94 states:

Statin therapy is recommended for adults with clinical evidence of CVD.

1.2 Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. This level of CVD risk should be estimated using an appropriate risk calculator, or by clinical assessment for people for whom an appropriate risk calculator is not available (for example, older people, people with diabetes or people in high-risk ethnic groups).

1.3 Within the recommendations outlined in Section 1.1. and Section 1.2, the decision whether to initiate statin therapy should be made after an informed discussion between the responsible clinician and the individual about the risks and benefits of statin treatment, and taking into account additional factors such as comorbidities and life expectancy.

1.4 When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).
NICE has also published a Clinical Guideline on Lipid Modification (CG67).

**B: Estimate of eligible patients**

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients without diabetes eligible for statins for primary prevention of CVD</td>
<td>1,024,110</td>
<td>(1)</td>
</tr>
<tr>
<td>Number of patients with ACS persisting with statins for secondary prevention of CVD</td>
<td>1,013,506</td>
<td>(1)</td>
</tr>
<tr>
<td>Number of patients with CAD persisting with statins for secondary prevention of CVD</td>
<td>698,660</td>
<td>(1)</td>
</tr>
<tr>
<td>Total number of patients eligible to receive statins for primary and secondary prevention of CVD</td>
<td>2,736,276</td>
<td></td>
</tr>
</tbody>
</table>

**C: Estimated usage (volume)**

The proportions of patients prescribed each statin are taken from the costing template accompanying NICE TA94. Note that this costing template covers Atorvastatin, Pravastatin, Rosouvasatin and Simvastatin only. The prescribing of other statins is assumed to be proportionally less than 1%.

**D: For 2011**

Total number of patients eligible to receive statins for primary and secondary prevention of CVD | 2,781,683   |

**References**

NICE TA94 Costing template – see Epidemiology sheet for calculations


**Observed uptake**

These medicines are mainly used in primary care (over 97 per cent by cost). Only data from the primary ePACT systems was used.

**Results**
The table below shows expected and observed use and the ratio between them for 2010 and 2011. Observed use was 131 per cent higher than expected in 2010 and 137 per cent higher in 2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (DDDs)</th>
<th>Observed</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>998,740,740</td>
<td>2,311,601,981</td>
<td>2.31</td>
</tr>
<tr>
<td>2011</td>
<td>1,015,314,295</td>
<td>2,403,136,929</td>
<td>2.37</td>
</tr>
</tbody>
</table>

The charts below compare the observed and expected use for 2010 and 2011. The proportion of PCTs with a ratio of greater than one increased from 74.8 per cent in 2010 to 82.1 per cent in 2011.
The cost of simvastatin has fallen dramatically over recent years and so a chart of costs would be misleading in showing use. The chart below shows use in terms of DDDs and uses data from the PCA database covering primary care and hospital prescriptions dispensed in the community.
A: Summary

Trastuzumab is licensed for the treatment of (BNF 63):

- early breast cancer which over expresses human epidermal growth factor receptor-2 (HER2);

- in combination with paclitaxel or docetaxel, for metastatic breast cancer in patients with HER2-positive tumours who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate;

- in combination with an aromatase inhibitor, for metastatic breast cancer in postmenopausal patients with hormone-receptor positive HER2-positive tumours not previously treated with trastuzumab;

- as monotherapy for metastatic breast cancer in patients with tumours that overexpress HER2 who have received at least 2 chemotherapy regimens including, where appropriate, an anthracycline and a taxane (women with oestrogen-receptor-positive breast cancer should also have received hormonal therapy).

Trastuzumab is also licensed, in combination with capecitabine or fluorouracil and cisplatin, for metastatic gastric cancer in patients with HER2-positive tumours who have not received treatment for metastatic gastric cancer.

Trastuzumab has been appraised by NICE for the treatment of advanced breast cancer (NICE technology appraisal guidance 34, NICE technology appraisal guidance 34, 2002):

Trastuzumab in combination with paclitaxel (combination trastuzumab is currently only licensed for use with paclitaxel) is recommended as an option for people with tumours expressing human epidermal growth factor receptor 2 (HER2) scored at levels of 3+ who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate.

Trastuzumab monotherapy is recommended as an option for people with tumours expressing HER2 scored at levels of 3+ who have received at least two chemotherapy regimens for metastatic breast cancer. Prior chemotherapy must have included at least an anthracycline and a taxane where these treatments are appropriate. It should also have included hormonal therapy in suitable oestrogen receptor positive patients.

NICE Clinical Guideline 81 on advanced breast cancer was published in 2009 but does not supersede TA34.

Trastuzumab has also been appraised for the treatment of early breast cancer (NICE technology appraisal TA107, 2006):
Offer trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to women with HER2-positive early invasive breast cancer following surgery, chemotherapy, and radiotherapy when applicable.

Recommendations relating to the treatment of early breast cancer have also been incorporated into the NICE Clinical Guideline 80 on early breast cancer.

Trastuzumab, in combination with cisplatin and capecitabine or 5-fluorouracil, is recommended as an option for the treatment of people with human epidermal growth factor receptor 2 (HER2)-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who:

- have not received prior treatment for their metastatic disease and
- have tumours expressing high levels of HER2 as defined by a positive
  immunohistochemistry score of 3 (IHC3 positive).

B: Estimate of eligible patient population

**Early stage and locally advanced breast cancer**

- Incidence of breast cancer (females) 39,681 (1)

- Women with early and locally advanced invasive breast cancer (stages I-III) 37,697 (95%) (2)
- HER2 positive patients 5,278 (14%) (3)
- Patients suitable for adjuvant treatment 4,797 (90.9%) (4)

- Unsuitable for treatment due to risk of adverse reaction 187 (3.9%) (5)

**Total suitable early stage patients for treatment with trastuzumab** 4,610

**Advanced breast cancer**

- Mortality (surrogate for metastatic breast cancer incidence) 10,065 (6)

- Metastatic breast cancer patients with HER2 over-expression 2,315 (23%) (7)
- Unsuitable for treatment due to risk of adverse reaction 231 (10%) (8)

**Total suitable advanced stage patients for treatment with trastuzumab** 2,083
### C: Estimated usage (volume)

**Early stage and locally advanced breast cancer:**

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average patient weight</td>
<td>70.7 kg</td>
<td>(9)</td>
</tr>
<tr>
<td>Loading dose</td>
<td>8 mg/kg</td>
<td>(10)</td>
</tr>
<tr>
<td>Number of vials (loading dose, rounded up)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>6 mg/kg</td>
<td>(10)</td>
</tr>
<tr>
<td>Number of vials (maintenance dose, rounded up)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Average number of maintenance doses</td>
<td>15.4</td>
<td>(11)</td>
</tr>
<tr>
<td>Total number of vials per course</td>
<td>50.2</td>
<td></td>
</tr>
<tr>
<td>Average volume per course</td>
<td>7,530 mg</td>
<td></td>
</tr>
</tbody>
</table>

**Estimated total volume (early stage and locally advanced BC)** $3.33 \times 10^7$ mg

**Advanced breast cancer:**

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average patient weight</td>
<td>70.7 kg</td>
<td>(9)</td>
</tr>
<tr>
<td>Loading dose</td>
<td>8 mg/kg</td>
<td>(10)</td>
</tr>
<tr>
<td>Number of vials (loading dose, rounded up)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>6 mg/kg</td>
<td>(10)</td>
</tr>
<tr>
<td>Number of vials (maintenance dose, rounded up)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Average number of maintenance doses</td>
<td>12.2</td>
<td>(12)</td>
</tr>
<tr>
<td>Total number of vials per course</td>
<td>40.6</td>
<td></td>
</tr>
<tr>
<td>Average volume per course</td>
<td>6,090 mg</td>
<td></td>
</tr>
</tbody>
</table>

**Estimated total volume (advanced stage BC)** $1.27 \times 10^7$ mg

**Total volume (early stage and locally advanced + advanced)** $4.74 \times 10^7$ mg

It is not anticipated that the estimated number of patients will be treated, or volume of medicine used, immediately following publication of guidance. It may, for example, be a period of time before patients present for treatment and this level is reached.

### D: For 2011

**Estimate of eligible patients**
**Early stage and locally advanced breast cancer**

Total suitable early stage patients for treatment with trastuzumab 4,677

**Advanced breast cancer**

Total suitable advanced stage patients for treatment with trastuzumab 2,392

**Gastric Cancer**

Total population 52,234,000 (1)

Estimated annual cases of gastric cancer 15,783 (2)

Estimated proportion of people presenting with cancer of the gastro-oesophageal junction or stomach 60.00% (3)

Number of people presenting with locally advanced or recurrent gastric cancer 9,470

Proportion of people presenting with metastatic disease 73.00% (4)

Number of people presenting with metastatic disease 6,913

Estimated proportion who are HER2-positive 16.88% (4)

Number of people who are HER2-positive 1,167

Proportion of people who have an immunohistochemistry score of 3 (IHC3) 62.56% (5)

Number of people who have IHC3 positive score 730

Proportion who have not had prior treatment and who would be able to receive trastuzumab combination therapy 53.00% (6)

**Estimated number of people who may be treated with trastuzumab** 387
### Estimate of usage (volume)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean patient weight (Kg)</td>
<td>62</td>
<td>(7)</td>
</tr>
<tr>
<td>Loading dose (mg/Kg)</td>
<td>8</td>
<td>(8)</td>
</tr>
<tr>
<td>Maintenance dose (mg/Kg)</td>
<td>6</td>
<td>(8)</td>
</tr>
<tr>
<td>No. of doses per patient (total loading + maintenance)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>No. loading doses</td>
<td>1</td>
<td>(7)</td>
</tr>
<tr>
<td>No. maintenance doses per course</td>
<td>7</td>
<td>(7)</td>
</tr>
<tr>
<td>Loading dose per average patient</td>
<td>496</td>
<td></td>
</tr>
<tr>
<td>Maintenance dose per patient (mg)</td>
<td>372</td>
<td></td>
</tr>
<tr>
<td>Total loading dose volume (mg)</td>
<td>496</td>
<td></td>
</tr>
<tr>
<td>Total maintenance dose volume (mg)</td>
<td>2,604</td>
<td></td>
</tr>
<tr>
<td>Number of Vials (150mg) loading</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Number of Vials (150mg) maintenance</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Total volume (mg) per course</td>
<td>3,100</td>
<td></td>
</tr>
</tbody>
</table>

### Estimated usage (volume)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total volume (early stage and locally advanced + advanced)</td>
<td>$4.98 \times 10^7$ mg</td>
</tr>
<tr>
<td>Total volume (gastric cancer)</td>
<td>$1.20 \times 10^7$ mg</td>
</tr>
<tr>
<td>Total volume</td>
<td>$5.10 \times 10^7$ mg</td>
</tr>
</tbody>
</table>
References (Breast Cancer)

1. Office for National Statistics, Cancer Statistics registrations: Registrations of cancer diagnosed in 2007, England. Series MB1 no.38. 2010, National Statistics: London. Incidence of breast cancer in males was 243 (is 0.6% of the total incidence) and is ignored in the above calculations.

2. Estimated incidence of de novo stage IV breast cancer in UK is 5.2% (Remak and Brazil, 2004. British Journal of Cancer, 91, 77 – 83). Remaining proportion of newly diagnosed patients Stage I-III (94.8%).


4. Double helix patient record card study 2010. A survey of 100 oncologists. Data supplied by Roche Products Ltd. The study identified patients with severe CV comorbidities, those patients who are node negative with tumours under 1 cm, those with contraindications to treatment and those who did not receive chemotherapy (reflective of current clinical practice for all those patients that would not be considered for chemotherapy or trastuzumab treatment).

5. Double helix patient record card study 2010. A survey of 100 oncologists. Data supplied by Roche Products Ltd. The study indicates that 96.1% of patients who have received chemotherapy will go on to be initiated on trastuzumab.


8. F) Double helix patient record card study 2010. A survey of 100 oncologists. Data supplied by Roche Products Ltd. The study indicates that 6% of women are ineligible for treatment with trastuzumab due to cardiovascular comorbidity. Clinical opinion indicates that higher number of patients will not be treated due to old age, frailty, inability to tolerate chemotherapy and patient choice. Therefore the figure has been revised to 10%.

9. The average body weight is a weighted average based on mean weight of females obtained from the Health Survey Tables of 2006 and applied to the cancer registrations of 2006 for each age group. Source: Costing template accompanying NICE TA107.

10. Herceptin Summary of Product Characteristics (http://www.medicines.org.uk/emc/). Early and metastatic breast cancer: Initial loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes.
11. Double helix patient record card study 2010. A survey of 100 oncologists. Data supplied by Roche Products Ltd. This indicates an average number of doses as 16.4 (1 loading dose and 15.4 maintenance doses), giving an effective average DOT of 49 weeks. The number allows for early treatment discontinuations.

12. Double helix patient record card study 2010. A survey of 100 oncologists. Data supplied by Roche Products Ltd. This indicates a mean duration of treatment to progression of 40 weeks (equivalent to 1 loading dose and 12.2 maintenance doses). This value fully accounts for both early discontinuation of treatment in some patients, and extended treatment to progression in others.

References (Gastric Cancer)


Observed uptake

This drug is used primarily in secondary care but the manufacturer (Roche) felt that the data collected by IMS Health was incomplete, partly because of homecare use and partly because of problems collecting data where aseptic units were involved. They therefore provided their own usage data at national, SHA and Cancer Network level for this analysis.

Results

The table below shows expected and observed use (data from Roche) and the ratio between them for 2010 using the expected number of patients with early or advanced breast cancer. On this basis observed use was 11 per cent lower than expected in 2010.
The table below shows expected and observed use and the ratio between them for 2011 using the expected number of patients with early or advanced breast cancer and gastric cancer. On this basis observed use was 14 per cent lower than expected in 2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (mg)</th>
<th>Observed (mg)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>47,400,000</td>
<td>42,363,229</td>
<td>0.89</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (mg)</th>
<th>Observed (mg)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>50,989,325</td>
<td>43,821,358</td>
<td>0.86</td>
</tr>
</tbody>
</table>

The charts below compare the observed and expected use for 2010 and 2011 at SHA level. Note that different expected values are used for each year as the 2011 estimates include use for gastric cancer,
The charts below show the ratios for Cancer Networks for 2010 and 2011. Note that different expected values are used for each year as the 2011 estimates include use for gastric cancer.
The chart below shows the cost for trastuzumab taken from the HPAI database for hospital use. As noted earlier, this is likely to be an underestimate because of missing homecare data.
Carmustine Implants

A: Summary

Carmustine implants are licensed for intraliesional use in adults for the treatment of recurrent glioblastoma multiforme as an adjunct to surgery. Carmustine implants are also licensed for high-grade malignant glioma as adjunctive treatment to surgery and radiotherapy.

NICE has appraised carmustine implants in TA121:

*Carmustine implants are recommended as a possible treatment for people with newly diagnosed high-grade glioma only if 90% or more of their tumour has been removed. People should have carmustine implants only at specialist treatment centres under the care of a team of experts, as described in ‘Improving outcomes for people with brain and other central nervous system tumours’ (NICE cancer service guidance 2006; www.nice.org.uk/csgbraincns).*

*Treatment should be supervised by specialist neurosurgeons who:*

- spend at least half of their time working in surgery to treat cancers of the brain and spinal cord
- work with a team of other specialists and have access to magnetic resonance imaging (MRI) to help predict before the operation whether it will be possible to remove 90% of the person’s tumour
- have access to technology that helps them precisely locate the tumour during the operation.

*Carmustine implants are not recommended for people with newly diagnosed high-grade glioma if less than 90% of their tumour has been removed.*

B: Estimate of eligible patients

<table>
<thead>
<tr>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
</tr>
<tr>
<td>Mean annual incidence of high-grade glioma per 100,000</td>
</tr>
<tr>
<td>Estimated annual number of new cases</td>
</tr>
</tbody>
</table>

| % of which have grade 3 glioma | 25% | (3) |
| % of which have grade 4 glioma (GBM) | 75% | (3) |

Grade 3 glioma

<table>
<thead>
<tr>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of grade 3 glioma</td>
</tr>
<tr>
<td>% of patients that undergo surgery</td>
</tr>
<tr>
<td>Number receiving surgery</td>
</tr>
</tbody>
</table>

% undergoing surgery in whom 90% has been resected | 25% | (5) |
Number eligible to receive carmustine implant

% of patients choosing to receive carmustine implants

Number of grade 3 patients to receive carmustine implants

Average number of implants per patient

Grade 4 glioma (GBM)

Number of grade 4 glioma

% of GBM patients with WHO status of 0 of 1

Number of GBM patients with WHO status of 0 or 1 (therefore eligible)

Estimated % of grade 4 patients that would receive carmustine implants

Estimated number of grade 4 that would receive carmustine implants

Average number of implants per patient

Total number of patients (grade 3 & grade 4) receiving implants

Total number of implants

Grade 3 Glioma

Grade 4 Glioma

C: Estimated usage (volume)

7.1\times10^3 mg

D: For 2011

Estimate of eligible patients:

Grade 3 Glioma

Grade 4 Glioma

Total

Estimated usage (volume):

7.14\times10^3 mg

References


2. Annual incidence data have been taken from the NICE assessment report
3. The ratio of grade 3 and grade 4 gliomas has estimated using an unpublished regional database covering a population of approximately 2.2 million. The data from this database is consistent with clinical consensus, in that grade 3 gliomas represent about 15% of high grade gliomas and anaplastic oligos (AO) represent about 5% - For the purpose of this report AO gliomas have been grouped together with grade 3 gliomas. Following expert opinion it is assumed that grade 4 (GBM) account for 75% of all gliomas with grade 3 and AO accounting for the rest.

4. Stupp et al 2005, Radiotherapy plus concomitant and adjuvant temozolomide for newly diagnosed glioblastoma

5. Expert opinion: the estimated percentage of patients in which 90% of the tumour can be resected would vary between 10 and 40%; for the purpose of this report a figure of 25% has been used.

5.a Although patients that have had 90% or more of their tumour resected would be eligible to receive carmustine implants it is estimated a proportion won’t receive the treatment. The figure of 39% is based on “NICE Guidance on the Use of Carmustine Wafers in High Grade Gliomas: A National Study on Variation in Practice”, Price S et al, submitted for publication to European Journal of Neurosurgery - in Press. Manuscript supplied by the manufacturer.

6. The manufacturer submission estimates the average number received to be 6.54, although estimates vary from 6 to 8 implants per patient.

7. Expert opinion: the estimated percentage of patients with a WHO status of 0 or 1 ranged from 40 to 60%; for the purpose of this report a figure of 50% has been used.

8. The guidance states that only those patients with a WHO status of 0 or 1 are eligible for this treatment.

9. Expert opinion suggests that a minority of the grade 4 patients would receive carmustine implants, estimated at being 15%. 85% would be treated with temozolomide.

10. Each implant contains 7.7mg of carmustine. (NICE TA121)

**Observed uptake**

This drug is used primarily in secondary care and so data was taken only from the HPAI database.

**Results**

The table below shows expected and observed use and the ratio between them for 2010 and 2011. The number of implants was 10 per cent higher than expected in 2010 and 26 per cent higher in 2011.
<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (implants)</th>
<th>Observed (implants)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>920</td>
<td>1,009</td>
<td>1.10</td>
</tr>
<tr>
<td>2011</td>
<td>928</td>
<td>1,173</td>
<td>1.26</td>
</tr>
</tbody>
</table>

The number of expected patients is quite low and so a sub-national analysis would not be appropriate.

The chart below shows the number of carmustine implants using data from the HPAI database of hospital use.

Carmustine Implants

[Graph showing the number of carmustine implants from Q2 2004 to Q1 2012 with a note indicating TA121 issued June 2007]
Prucalopride

A: Summary

Prucalopride is indicated for chronic constipation in women when other laxatives fail to provide an adequate response (BNF 63).

NICE TA211 recommends prucalopride as an option for the treatment of chronic constipation only in women for whom treatment with at least two laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and invasive treatment for constipation is being considered.

- If treatment with prucalopride is not effective after 4 weeks, the woman should be re-examined and the benefit of continuing treatment reconsidered.
- Prucalopride should only be prescribed by a clinician with experience of treating chronic constipation, who has carefully reviewed the woman’s previous courses of laxative treatments specified in 1.

B: Estimate of eligible patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Total Population</th>
<th>Estimated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>51,809,700</td>
<td></td>
</tr>
<tr>
<td>Women aged 18–64</td>
<td>16,231,979</td>
<td></td>
</tr>
<tr>
<td>Women aged 65 and over</td>
<td>4,719,864</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th>Proportion</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of women aged 18–64 with chronic constipation</td>
<td>7.70%</td>
<td>1,249,862</td>
</tr>
<tr>
<td>Proportion of women aged 65 and over with chronic constipation</td>
<td>20.00%</td>
<td>943,973</td>
</tr>
<tr>
<td>Proportion of women with chronic constipation aged 18–64 presenting to a GP</td>
<td>70.00%</td>
<td>874,904</td>
</tr>
<tr>
<td>Proportion of women aged 65 and over with chronic constipation presenting to a GP</td>
<td>70.00%</td>
<td>660,781</td>
</tr>
<tr>
<td>Proportion of those women aged 18–64 for whom laxatives fail to provide adequate relief</td>
<td>10.00%</td>
<td>87,490</td>
</tr>
<tr>
<td>Proportion of those women aged 65 and over for whom laxatives fail to provide adequate relief</td>
<td>10.00%</td>
<td>66,078</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>153,568</td>
</tr>
<tr>
<td>Proportion of those women for whom second course of laxatives fail</td>
<td>50.00%</td>
<td>76,784</td>
</tr>
</tbody>
</table>
Patients for whom two courses of laxatives and 6 months treatment have failed and prucalopride could be prescribed 50.00% 38,392 (4)

Patients considered for prucalopride 100.00% 38,392 (5)
Percentage treated with prucalopride 25.00% 9,598 (5)

C: Estimated Usage (volume)

WHO DDD for Prucalopride 2mg (6)

Total number of mg (220 days) 4.22x10^6

It is not anticipated that the estimated number of patients will be treated, or volume of medicine used, immediately following publication of guidance. It may, for example, be a period of time before patients present for treatment and this level is reached.

References


2. Based on manufacturer’s submission 2010. Incidence of 7.7% with chronic constipation. 60-70% present to their GP.

3. Clinical specialist opinion.

4. Clinical specialist opinion that 50% patients do not have adequate response to a current second course of laxatives. Subsequent courses result in decreasing response.

5. As per Final Appraisal Determination. Prucalopride prescribed following treatment with at least two laxatives from different classes. 25% take up rate assumed in year 1.

6. WHO ATC/DDD index http://www.whocc.no/atc_ddd_index/

Observed uptake

This drug is used in all sectors and so data was taken both versions of ePACT and from the HPAI database.
Results

The appraisal was issued in December 2010 and so a comparison has only been done for 2011. The table below shows expected and observed use and the ratio between them for 2011. The use was 89 per cent lower than expected in 2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (DDDs)</th>
<th>Observed (DDDs)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>4,220,000</td>
<td>450,160</td>
<td>0.11</td>
</tr>
</tbody>
</table>

The chart below compares the observed and expected use for 2011 at SHA level.

The chart below shows the net ingredient cost by quarter for England. Data is taken from the PCA database (which covers both primary care and prescriptions issued in hospitals and dispensed in the community) and the IMS Health HPAI system which covers hospital use.
Febuxostat

A: Summary

Febuxostat is licensed for the treatment of chronic hyperuricaemia where urate deposition has already occurred; it is not indicated for patients in whom the rate of urate formation is greatly increased, such as in malignant disease or in Lesch-Nyhan syndrome.

NICE TA164 states: *Febuxostat is recommended as an option for the management of chronic hyperuricaemia in gout only for patients who are intolerant of allopurinol or for whom allopurinol is contra-indicated.*

For the purposes of this guidance, intolerance of allopurinol is defined as adverse effects that are sufficiently severe to warrant discontinuation, or to prevent full dose escalation for optimal effectiveness.

B: Estimate of eligible patients

England population 51,806,700 (1)

UK Prevalence of gout 1.5% (2)

Total cases of gout 777,146 (2)

Estimated proportion and number of patients with gout eligible for receiving urate-lowering drugs 61% (3)

Estimated average number of patients contraindicated to or intolerant of allopurinol 5% (4)

Treatment for people contraindicated to or intolerant of allopurinol

Sulphinpyrazone (6%) 1,422 (5)

Febuxostat* (94%) 22,281 (5)

*This percentage breakdown is based on the assumption that following the TA all patients not currently receiving therapy will be offered febuxostat. A proportion of those patients offered treatment will decline therapy; however this quantity is unknown at present.
C: Estimated usage (volume)

Daily dose per patient 80 mg (6)

Total Estimated volume $6.51 \times 10^8$ mg

It is not anticipated that the estimated number of patients will be treated, or volume of medicine used, immediately following publication of guidance. It may, for example, be a period of time before patients present for treatment and this level is reached.

D: For 2011

Estimate of eligible patients: 22,463

Estimated usage (volume): $6.56 \times 10^8$

References


3. The average proportion of patients eligible for urate-lowering treatment is based on the proportion who have had two or more gout flare-ups in 12 months. This was obtained from Mandell BF (2008) Clinical manifestations of hyperuricaemia and gout. Cleveland Clinical Journal of Medicine 75 (Suppl. 5) S5–8: (60%) and Siresh E (2005) Diagnosis and management of gout: a rational approach. Postgrad Med Journal 81: 572–579 (62%).

4. The number of people contraindicated to or intolerant of allopurinol is estimated as 3%. This was obtained from Andrew Alldred (2005) Gout - pharmacological management. Hospital Pharmacist November 2005; 12 (3–5%) and Gutiérrez-Macías A, Lizarralde-Palacios E, Martínez-Odriozola P et al. (2005) Fatal allopurinol hypersensitivity syndrome after treatment of asymptomatic hyperuricaemia. British Medical Journal 331: 623–624 (2%). Available from: www.bmj.com/cgi/content/full/331/7517/623

5. The number of people currently receiving sulphinpyrazone is based on the average annual prescription cost as per 2006–07 Prescription Costs Analysis, which is then applied to the estimated proportion of patients contraindicated to allopurinol. Other therapies, such as probenecid, are available on a named person basis (hence numbers are very small) and benz bromarone has very limited availability.

6. WHO DDD Index
Observed uptake

This drug is used in all sectors and so data was taken both versions of ePACT and from the HPAI database.

Results

The table below shows expected and observed use and the ratio between them for 2010 and 2011. The use was 97 per cent lower than expected in 2010 and 90 per cent lower in 2011. This estimate is based on the assumption that following the TA all patients not currently receiving therapy will be offered febuxostat. A proportion of those patients offered treatment will decline therapy; however this quantity is unknown at present but will impact on this comparative analysis.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (DDDs)</th>
<th>Observed (DDDs)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>8,132,200</td>
<td>229,020</td>
<td>0.03</td>
</tr>
<tr>
<td>2011</td>
<td>8,198,995</td>
<td>836,206</td>
<td>0.10</td>
</tr>
</tbody>
</table>

The charts below compare the observed and expected use for 2010 and 2011 at SHA level.
The chart below shows the net ingredient cost by quarter for England. Data is taken from the PCA database (which covers both primary care and prescriptions issued in hospitals and dispensed in the community) and the IMS Health HPAI system which covers hospital use.
This section of results includes the following medicines/groups of medicines:

- Pioglitazone
- Breast cancer (early) - hormonal treatments (anastrozole, exemestane, letrozole)
- Capecitabine
- Gefitinib
- Omalizumab
- Peginterferon Alfa-2a and 2b for hepatitis C
- Sunitinib
- Alzheimers
- Ezetimibe
- Erlotinib
- Alitretinoin

This report is classed as an “Experimental Statistics” report. This means that the statistics held within it are constantly subject to evaluation and have many uncertainties and caveats associated with them. Where these caveats can be reasonably well defined and detailed, and there still remains the ability to compare estimated and observed usage, a medicine will fall under section 1 of this report. Where these caveats prevent that comparison from being made, or are so statistically significant as to render a comparison potentially misleading, then it is not appropriate to include a medicine in section 1. The purpose of section 2 is to highlight case study examples of the methodological complications of this work and to detail selected medicines where a comparison between estimated and observed usage cannot be made, along with a description of why this is the case. Medicines in this section are still subject to the experimental statistics label, but any figures presented in this section must be treated with lower confidence than those presented in section 1 and with particular attention to the uncertainties and issues highlighted in the boxes at the end of each estimate. Where it has been possible to attempt a comparative analysis, this has been at a more restricted geographical scale than section 1.

A key part of the “Experimental statistics” label is user engagement in the evaluation of those statistics, the NHS IC invites readers to comment on experimental publications, which will help inform the next report. With this in mind, a series of consultation questions pertaining to each medicine in this section are detailed at the end of each estimate. It is hoped that feedback on these section 2 medicines will enable further work to be done in the future to increase confidence in these estimates.

Some medicines have many interlocking factors which preclude any analysis, and have therefore been excluded from the report. These are detailed in appendix A along with selected examples which highlight the rationale behind their exclusion.
Pioglitazone and rosiglitazone for the treatment of type 2 diabetes

A: Summary

Pioglitazone reduces peripheral insulin resistance, leading to a reduction of blood-glucose concentration. NICE Clinical Guideline 87 recommended that, when glycaemic control is inadequate with existing treatment, a thiazolidinedione can be added to:

- a sulphphonylurea, if metformin is contra-indicated or not tolerated;
- metformin, if risks of hypoglycaemia with sulphphonylurea are unacceptable or a sulphphonylurea is contra-indicated or not tolerated;
- a combination of metformin and a sulphphonylurea, if insulin is unacceptable because of lifestyle or other personal issues, or because the patient is obese.

NICE has recommended that treatment with a thiazolidinedione is continued only if HbA1c concentration is reduced by at least 0.5% within 6 months of starting treatment. In July 2011, The European Medicines Agency advised that there is a small increased risk of bladder cancer associated with pioglitazone use. However, in patients who respond adequately to treatment, the benefits of pioglitazone continue to outweigh the risks. Pioglitazone should not be used in patients with active bladder cancer or a past history of bladder cancer, or in those who have uninvestigated macroscopic haematuria. Pioglitazone should be used with caution in elderly patients as the risk of bladder cancer increases with age. Before initiating treatment with pioglitazone, patients should be assessed for risk factors of bladder cancer (including age, smoking status, exposure to certain occupational or chemotherapy agents, or previous radiation therapy to the pelvic region) and any macroscopic haematuria should be investigated. The safety and efficacy of pioglitazone should be reviewed after 3–6 months and pioglitazone should be stopped in patients who do not respond adequately to treatment. Patients already receiving treatment with pioglitazone should be assessed for risk factors of bladder cancer and treatment should be reviewed after 3–6 months, as above. Patients should be advised to report promptly any haematuria, dysuria, or urinary urgency during treatment.

The marketing authorisation for rosiglitazone has been suspended (September 2010) following a review by the European Medicines Agency. The European Medicines Agency concluded that the benefits of rosiglitazone treatment do not outweigh the cardiovascular risks. Prescribers should not issue new or repeat prescriptions for rosiglitazone. Treatment of patients who are taking rosiglitazone should be reviewed.

This estimate takes the above factors into consideration and presents numbers of eligible patients for both drugs in 2010 (noting the withdrawal of rosiglitazone in September) and for pioglitazone only in 2011.

B: Estimate of eligible patients

<table>
<thead>
<tr>
<th>England population (17 years or older)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>41,464,40</td>
</tr>
</tbody>
</table>

(1)
Diabetes prevalence in England (17 years or older) 5.4% 2,239,078 (2)
Proportion of diabetes patients with type 2 diabetes (17 years or older) 90% 2,015,170 (3)
Type 2 diabetes patients in England < 17 years 328 (4)
Total type 2 diabetes patients (all ages) 2,015,498
Estimated number of patients eligible for pioglitazone 9% 181,395 (5)
Estimated number of patients eligible for rosiglitazone till September 2010 3% 70,542 (5)

C: Estimated usage (volume)

WHO DDD for pioglitazone: 30 mg

WHO DDD for Rosiglazone: 6mg

Rosiglitazone volume estimated over period 1/1/2010 to 1/9/2010 1.54x10^8 mg

Pioglitazone volume for 2010 (assuming all patients switch following rosiglitazone withdrawal in September) 2.93x10^9 mg

D: Usage in 2011

Pioglitazone assuming all rosiglitazone patients switched (estimated for full year but likely to be impacted by pioglitazone safety concerns post July 2011) 2.95x10^9 mg

It is not anticipated that the estimated number of patients will be treated, or volume of medicine used, immediately following publication of guidance. It may, for example, be a period of time before patients present for treatment and this level is reached.

References


(3) Department of Health (2007). About diabetes

(4) Growing up with Diabetes: children and young people with diabetes in England.
March 2009. Royal College of Paediatrics and Child Health.
(www.rcpch.ac.uk/doc.aspx?id_Resource=4817)

(5) Estimated percentage of patients requiring thiazolidinediones as 1st-4th line

treatment:

  Pioglitazone (total 9%): 1st line Pioglitazone (1%), 2nd line metformin & pioglitazone
  (3%), 2nd line sulfonylurea & pioglitazone (1.5%), 3rd line metformin & sulfonylurea &
  pioglitazone (3.5%).

  Rosiglitazone (total 3.5%): 1st line rosiglitazone (0%), 2nd line metformin &
  rosiglitazone (1%), 2nd line sulfonylurea & rosiglitazone (0.5%), 3rd line metformin &
  sulfonylurea & rosiglitazone (2%).

  Source: Pharmacological treatments within the costing template accompanying NICE
  CG87.

**Observed uptake**

This medicine is used almost entirely in primary care and so only primary care data has been

used.

**Results**

The table below shows expected and observed use and the ratio between them for 2010 and

2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected</th>
<th>Observed</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>66,209,175</td>
<td>54,770,159</td>
<td>0.83</td>
</tr>
<tr>
<td>2011</td>
<td>66,209,175</td>
<td>62,974,146</td>
<td>0.95</td>
</tr>
</tbody>
</table>

It must be noted that in 2010 the competing product rosiglitazone was also available (this

was withdrawn in September 2010). There were over 20 million DDDs of rosiglitazone

dispensed in 2010. If these figures are added to the pioglitazone figure then the ratio for

2010 would be 1.13, which is 13% higher than expected.

The chart below shows the cost of pioglitazone using data from the Prescription Cost

Analysis database.
The following chart shows the cost of the sum of pioglitazone and rosiglitazone costs using data from the PCA database.

### Issues

These medicines have been placed in section 2 because of the safety concerns raised in both 2010 and 2011 which will have affected their usage. Rosiglitazone was withdrawn in 2010, but the safety concerns from the EMA identified for pioglitazone are difficult to assess in terms of their impact on prescribing.

### Question for consultation

1) How can the number of patients with risk factors which would contraindicate pioglitazone use be estimated?
Breast cancer (early) - hormonal treatments (anastrozole, exemestane, letrozole)

A: Summary

Anastrazole is indicated for:
- adjuvant treatment of oestrogen-receptor-positive early invasive breast cancer in postmenopausal women;
- adjuvant treatment of oestrogen receptor-positive early breast cancer in postmenopausal women following 2–3 years of tamoxifen therapy;
- Advanced breast cancer in postmenopausal women which is oestrogen receptor-positive or responsive to tamoxifen.

Exemestane is indicated for:
- adjuvant treatment of oestrogen-receptor-positive early breast cancer in postmenopausal women following 2–3 years of tamoxifen therapy;
- Advanced breast cancer in postmenopausal women in whom anti-oestrogen therapy has failed.

Letrozole is indicated for:
- adjuvant treatment of oestrogen-receptor-positive early breast cancer in postmenopausal women;
- advanced breast cancer in postmenopausal women (including those in whom other anti-oestrogen therapy has failed);
- early invasive breast cancer in postmenopausal women after standard adjuvant tamoxifen therapy;
- Pre-operative treatment in postmenopausal women with localised hormone-receptor-positive breast cancer to allow subsequent breast conserving surgery (BNF 63)

Relevant guidance

NICE Technology Appraisal 112 ‘Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer’.

- The aromatase inhibitors anastrozole, exemestane and letrozole, within their licensed indications, are recommended as options for the adjuvant treatment of early oestrogen receptor-positive invasive breast cancer in postmenopausal women.
## B: Estimate of eligible patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer incidence</td>
<td>40,260</td>
<td>(1)</td>
</tr>
<tr>
<td>% of patients with stage I and II early breast cancer</td>
<td>32,208 (80%)</td>
<td>(2)</td>
</tr>
<tr>
<td>% of patients with oestrogen-receptor positive tumours</td>
<td>28,665 (89%)</td>
<td>(3)</td>
</tr>
<tr>
<td>% of patients suitable for surgery and therefore adjuvant treatment</td>
<td>25,512 (89%)</td>
<td>(4)</td>
</tr>
</tbody>
</table>

### Adjuvant treatment options

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
<th>Patients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td><strong>Primary adjuvant therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continuation with tamoxifen for 5 years</td>
<td>5,102 (20%)</td>
<td>(5)</td>
</tr>
<tr>
<td>B</td>
<td>5 years of anastrozole</td>
<td>5,102 (20%)</td>
<td>(5)</td>
</tr>
<tr>
<td>C</td>
<td>5 years of letrozole</td>
<td>5,102 (20%)</td>
<td>(5)</td>
</tr>
<tr>
<td>D</td>
<td><strong>Unplanned switch therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 years of tamoxifen followed by 3 years of exemestane</td>
<td>10,205 (40%)</td>
<td>(5)</td>
</tr>
<tr>
<td>A2</td>
<td><strong>Extended adjuvant therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 years of letrozole (following tamoxifen primary adjuvant therapy)</td>
<td>10,215 (50%)</td>
<td>(5)</td>
</tr>
</tbody>
</table>
C: Estimated usage (volume)

TA112 was published in November 2006. The NICE costing template published at the same point indicated how medicine usage would change over time. As 2010 and 2011 usage is being looked at, estimated usage is expected to be at the year 4 and 5 figures listed below.

### A1: Primary adjuvant therapy: Continuation with tamoxifen for 5 years (based on TA112 costing template)

<table>
<thead>
<tr>
<th>Year</th>
<th>Year 0</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients starting this year</td>
<td>5102</td>
<td>5102</td>
<td>5102</td>
<td>5102</td>
<td>5102</td>
<td>5102</td>
<td></td>
</tr>
<tr>
<td>Patients stopping this year</td>
<td>25,512</td>
<td>25,512</td>
<td>25,512</td>
<td>25,512</td>
<td>25,512</td>
<td>5102</td>
<td></td>
</tr>
<tr>
<td>Total number of patients</td>
<td>127,560</td>
<td>107,150</td>
<td>86,740</td>
<td>66,330</td>
<td>45,920</td>
<td>25,510</td>
<td></td>
</tr>
</tbody>
</table>

### B: Primary adjuvant therapy: 5 years of anastrozole

<table>
<thead>
<tr>
<th>Year</th>
<th>Year 0</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients starting this year</td>
<td>5102</td>
<td>5102</td>
<td>5102</td>
<td>5102</td>
<td>5102</td>
<td>5102</td>
<td></td>
</tr>
<tr>
<td>Patients stopping this year</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5102</td>
<td></td>
</tr>
<tr>
<td>Total number of patients</td>
<td>0</td>
<td>5102</td>
<td>8,172</td>
<td>12,258</td>
<td>16,344</td>
<td>20,430</td>
<td></td>
</tr>
<tr>
<td>daily dose = 1 mg anastrozole tablet (6)</td>
<td>1 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total annual volume per patient</td>
<td>365 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total annual volume</td>
<td>1.86x10^6 mg</td>
<td>3.72x10^6 mg</td>
<td>5.59x10^6 mg</td>
<td>7.45x10^6 mg</td>
<td>9.31x10^6 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### C: Primary adjuvant therapy: 5 years of letrozole (based on TA112 costing template)

<table>
<thead>
<tr>
<th>Year</th>
<th>Year 0</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients starting this year</td>
<td>5102</td>
<td>5102</td>
<td>5102</td>
<td>5102</td>
<td>5102</td>
<td>5102</td>
<td></td>
</tr>
<tr>
<td>Patients stopping this year</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5102</td>
<td></td>
</tr>
<tr>
<td>Total number of patients</td>
<td>0</td>
<td>5102</td>
<td>10,204</td>
<td>15,306</td>
<td>20,408</td>
<td>25,510</td>
<td></td>
</tr>
<tr>
<td>daily dose = 2.5 mg letrozole tablet (6)</td>
<td>2.5 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total annual volume per patient</td>
<td>913 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total annual volume</td>
<td>4.66x10^6 mg</td>
<td>9.31x10^6 mg</td>
<td>1.40x10^7 mg</td>
<td>1.86x10^7 mg</td>
<td>2.33x10^7 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### D: Unplanned switch therapy : 2 years of tamoxifen followed by 3 years of exemestane (based on TA112 costing template)

<table>
<thead>
<tr>
<th>Year</th>
<th>Year 0</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>tamoxifen Patients starting this year</td>
<td>10205</td>
<td>10205</td>
<td>10205</td>
<td>10205</td>
<td>10205</td>
<td>10205</td>
<td></td>
</tr>
<tr>
<td>Patients stopping this year</td>
<td>0</td>
<td>0</td>
<td>10205</td>
<td>10205</td>
<td>10205</td>
<td>10205</td>
<td></td>
</tr>
<tr>
<td>Total number of patients</td>
<td>0</td>
<td>10205</td>
<td>16,334</td>
<td>16,334</td>
<td>16,334</td>
<td>16,334</td>
<td></td>
</tr>
<tr>
<td>exemestane Patients starting this year</td>
<td>10205</td>
<td>10205</td>
<td>10205</td>
<td>10205</td>
<td>10205</td>
<td>10205</td>
<td></td>
</tr>
<tr>
<td>Patients stopping this year</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10205</td>
<td>10205</td>
<td>10205</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Year 0</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2,551</td>
<td>2,551</td>
<td>2,551</td>
<td>2,551</td>
<td>2,551</td>
<td>2,551</td>
</tr>
</tbody>
</table>

**Tamoxifen**

*Figures for tamoxifen in this instance not included as focus on hormonal therapy*

**Letrozole**

<table>
<thead>
<tr>
<th>Patients starting this year</th>
<th>2,551</th>
<th>2,551</th>
<th>2,551</th>
<th>2,551</th>
<th>2,551</th>
<th>2,551</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients stopping this year</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2,551</td>
<td>2,551</td>
<td>2,551</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>0</td>
<td>2,551</td>
<td>5,102</td>
<td>7,653</td>
<td>7,653</td>
<td>7,653</td>
</tr>
</tbody>
</table>

*Daily dose = 25 mg letrozole tablet (6)*

<table>
<thead>
<tr>
<th>Total annual volume per patient</th>
<th>2.33x10^6 mg</th>
<th>4.66x10^6 mg</th>
<th>6.98x10^6 mg</th>
<th>6.98x10^6 mg</th>
<th>6.98x10^6 mg</th>
<th>6.98x10^6 mg</th>
</tr>
</thead>
</table>

**2010**

| Total volume for anastrozole | 7.45x10^6 mg |
| Total volume for letrozole   | 2.56x10^7 mg |
| Total volume for exemestane  | 2.79x10^8 mg |

**2011**

| Total volume for anastrozole | 9.31x10^6 mg |
| Total volume for letrozole   | 3.03x10^7 mg |
| Total volume for exemestane  | 2.79x10^8 mg |
References

1. Population figures for years 1 and 2 are based on the patient lists of GPs in practices affiliated to each primary care organisation and the ONS national population estimates inputted into costing template TA112.

2. The 'NHS Breast Screening Programme and association of breast surgery at BASO audit of screen detected breast cancers for the year of screening April 2004 to March 2005' states "Overall, 31% of invasive cancers were grade I, 49% were grade II, 18% were grade III and 2% were not assessable or unknown".


4. The 'NHS Breast Screening Programme and association of breast surgery at BASO audit of screen detected breast cancers for the year of screening April 2004 to March 2005' states "Of invasive cancers with known ER status, 89% were ER positive and 11% were ER negative" (where ER is oestrogen receptor). [http://www.cancerscreening.nhs.uk/breastscreen/publications/baso2004-2005.pdf](http://www.cancerscreening.nhs.uk/breastscreen/publications/baso2004-2005.pdf)

5. Estimated percentage of patients who are fit for surgery is taken from the assessment report. ([http://www.nice.org.uk/guidance/index.jsp?action=folder&o=33596](http://www.nice.org.uk/guidance/index.jsp?action=folder&o=33596))

6. Estimated uptake of the different hormonal therapies is based upon clinical opinion sought before the publication of the NICE costing report accompanying Technology Appraisal 112.

7. Doses taken from TA112 costing template and BNF 63

Observed uptake

These medicines are mainly used in primary care but data was taken from both versions of ePACT and the HPAI database.

Results

The table below shows the comparison between expected and observed use for 2010 and 2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (DDDs)</th>
<th>Observed (DDs)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>20,150,000</td>
<td>36,645,964</td>
<td>1.82</td>
</tr>
<tr>
<td>2011</td>
<td>18,570,000</td>
<td>37,680,497</td>
<td>2.03</td>
</tr>
</tbody>
</table>
The NICE appraisal, and hence the estimate, only covers use for early breast cancer but these drugs now have wider licenses. Accordingly no sub-national comparison has been made.

**Issue**

These medicines have been appraised by NICE for the treatment of early breast cancer. However they are also licensed for use in advanced breast cancer. No comparison between estimated and actual use can be made as usage data is not available by diagnosis.

**Questions**

1. How can the data on the use of these medicines be obtained by diagnosis / stage of disease and phase of treatment (1st line, 2nd line)?

2. If data cannot be obtained by diagnosis, how can an estimate of expected use be constructed where technology appraisal guidance on appropriate use of these medicines does not cover all indications?

3. Are there estimates of the relative proportions of early and advanced breast cancer (ideally at SHA/Cancer Network level) which could be used here?
Capecitabine

A: Summary

Capecitabine, which is metabolised to fluorouracil, is given by mouth. It is licensed as monotherapy or combination therapy for adjuvant treatment of advanced colon cancer following surgery, for monotherapy or combination therapy of metastatic colorectal cancer, and for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen. Capecitabine is also licensed for second-line treatment of locally advanced or metastatic breast cancer either in combination with docetaxel (where previous therapy included an anthracycline) or alone (after failure of a taxane and anthracycline regimen or where further anthracycline treatment is not indicated).

NICE CG81 states: For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence:

- first line: single-agent docetaxel
- second line: single-agent vinorelbine or capecitabine
- third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment).

NICE TA191 states: NICE recommends capecitabine, taken with platinum-containing drugs, for some people with stomach cancer.

You should be able to have capecitabine if:

- your stomach cancer is advanced and
- you have not had treatment for advanced stomach cancer before and
- your cancer cannot be removed with an operation.

NICE TA100 states: Capecitabine and oxaliplatin are recommended as possible adjuvant treatments after surgery for stage III (Dukes' C) colon cancer, when used in the following ways:

- capecitabine on its own
- oxaliplatin together with 5-fluorouracil and folinic acid.

The choice of treatment should be decided jointly by the individual and their doctors, after they have discussed the options. This discussion should cover any contraindications to the treatments (reasons why a particular medicine might not be suitable for the person), the possible side effects of the treatments, and the different ways they can be given. It should also take into account the person’s clinical condition and individual preferences.
B: Estimate of eligible patients

Estimate of eligible patients for NICE appraised indications

Given the information available, the emphasis on capecitabine as an option for treatment (amongst other medicines) and that the decision on the medicine should be made jointly between the clinician and patient, it has not been possible to develop an estimate.

Observed uptake

Roche, who manufacture this medicine, advised that the available data was inadequate and provided their own data.

Results

It was not possible to develop an estimate of use (as above). The results below therefore show the total use as recorded by Roche (in milligrams) divided by the recorded incidence in the period 2004 to 2006 (taken from the National Cancer e-atlas 2010) of colorectal cancer and breast cancer. Incidence rates are published for Cancer Networks but not SHAs and so results are shown only for Cancer Networks. Data for 2010 is presented as an illustration of variation.

<table>
<thead>
<tr>
<th>Cancer Network</th>
<th>Milligram of capecitabine per patient with breast or colorectal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anglia</td>
<td>0.40</td>
</tr>
<tr>
<td>Avon, Somerset &amp; Wiltshire</td>
<td>0.35</td>
</tr>
<tr>
<td>Kent &amp; Medway</td>
<td>0.30</td>
</tr>
<tr>
<td>Greater Manchester &amp; Greater Merseyside</td>
<td>0.25</td>
</tr>
<tr>
<td>Oxford</td>
<td>0.20</td>
</tr>
<tr>
<td>North East London</td>
<td>0.15</td>
</tr>
<tr>
<td>North West London</td>
<td>0.10</td>
</tr>
<tr>
<td>North of England</td>
<td>0.05</td>
</tr>
<tr>
<td>South West London</td>
<td>0.00</td>
</tr>
<tr>
<td>Surrey, West Sussex &amp; Hampshire</td>
<td>0.00</td>
</tr>
<tr>
<td>Thames Valley &amp; 3 Counties</td>
<td>0.00</td>
</tr>
<tr>
<td>Yorkshire</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Since other drugs are also licensed to treat these conditions, any variation may simply be related to the choice of drug and should not be taken to imply that patients are not being treated.
**Issue**
Capecitabine is recommended as an option for treatment as other medicines are available and should be considered equally.
As usage data is not available by diagnosis, no comparison is possible between estimated and observed usage.

**Consultation questions**

1. How can the data on the use of medicines by diagnosis be obtained?

2. If data cannot be obtained by diagnosis, how can an estimate of expected use be constructed where technology appraisal guidance on appropriate use of these medicines does not cover all indications?

3. Where a medicine is one treatment option amongst others, how can estimates and usage data account for alternative treatment options? This is a particularly difficulty in the case of cancer medicines. Also where the alternative options have multiple indications, their use is not available by diagnosis.
Gefitinib

A: Summary

NICE appraised gefitinib in 2010 in TA192, “Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer”. The guidance said

Gefitinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC) if:

- they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation and
- the manufacturer provides gefitinib at the fixed price agreed under the patient access scheme.

B: Estimate of eligible patients

It is not possible to produce an estimate for this drug. It was agreed that an estimate of the number of patients with non-small-cell lung cancer who also had the epidermal growth factor receptor tyrosine kinase mutation would be used as the best approximation of the number of patients likely to be eligible.

<table>
<thead>
<tr>
<th>Total population</th>
<th>51,810,970</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of lung cancer</td>
<td>0.06%</td>
</tr>
<tr>
<td>Proportion and number of confirmed non-small cell carcinoma</td>
<td>80%</td>
</tr>
<tr>
<td>Proportion and number of patients presenting with stage III (advanced) or stage IV (metastatic) non-small cell lung cancer</td>
<td>78.17%</td>
</tr>
<tr>
<td>Proportion and number of patients presenting with stage III or stage IV lung cancer who receive chemotherapy as first-line treatment</td>
<td>23%</td>
</tr>
<tr>
<td>Total number eligible to receive EGFR testing</td>
<td>4,535</td>
</tr>
<tr>
<td>Proportion and number of patients expected to have EGFR mutation status results that may be evaluated</td>
<td>60%</td>
</tr>
<tr>
<td>Proportion and number of patients expected to have a positive EGFR mutation status</td>
<td>15%</td>
</tr>
</tbody>
</table>

Observed uptake

AstraZeneca, who manufacture this medicine, advised that the data available to the HSCIC was incomplete and provided their own figures on the number of patients treated.
Results

For 2011 it has been estimated that there were 409 patients who might have been eligible for treatment with gefitinib while the company reported that 479 were treated.

Since patient numbers are so low a sub-national analysis is not appropriate.

Issue

Gefitinib is an option for treatment in patients with EGFR positive mutation status non-small cell lung cancer. Alternative therapy regimens exist and it is not known how the eligible patient population will be distributed across these options.

Consultation questions

1. How can an estimate of the proportion of patients being treated with the different options be produced?

2. What data exists to support this analysis?
**Omalizumab**

**A: Summary**

Omalizumab is a monoclonal antibody that binds to immunoglobulin E (IgE). It is used as additional therapy in individuals with proven IgE-mediated sensitivity to inhaled allergens, whose severe persistent allergic asthma cannot be controlled adequately with high-dose inhaled corticosteroid together with a long-acting beta\textsubscript{2} agonist. Omalizumab should be initiated by physicians in specialist centres experienced in the treatment of severe persistent asthma (BNF 63).

NICE TA133 states: *Omalizumab is recommended as a possible treatment for adults and young people over 12 years with severe persistent allergic asthma when all of the following circumstances apply.*

- When the person’s asthma is still severe and unstable despite best efforts to control it with other asthma medicines taken as directed by their doctor.
- When the person has stopped smoking, if their doctor feels it is appropriate.
- When the person has allergic asthma. This should be confirmed by checking past symptoms and skin testing for allergies.
- When the person has had at least two asthma attacks within the past year that have needed admission to hospital, or when the person has had three or more severe asthma attacks within the past year, one of which has needed admission to hospital and the other two have needed additional treatment in an accident and emergency department.

*Omalizumab treatment should be given along with the person’s current asthma medicines. It should be prescribed by a doctor who is experienced in asthma and allergy medicine at a specialist centre.*  
*If omalizumab does not control the asthma after 16 weeks, treatment should be stopped.*

NICE does not recommend omalizumab for children aged 6 to 11 years with severe persistent allergic asthma.

**B: Estimate of eligible patients**

Information from a costing template accompanying NICE Technology Appraisal TA133 ‘Omalizumab for severe persistent allergic asthma’.

<table>
<thead>
<tr>
<th></th>
<th>Individuals with ≥ 2 admissions to hospital for asthma in the past 12 months</th>
<th>9,815 (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Individuals with 1 admission to hospital for asthma in the past 12 months</td>
<td>41,587</td>
</tr>
</tbody>
</table>

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It is estimated that 24.5% of the above patients have been to A&E on 2 occasions

Subgroup of asthma population (A+B) 20,004

From above subgroup, patients with allergic asthma 11,602 (58%) (4)
Estimated number with IgE levels within range 9,200 (79.3%) (5)
Estimated number within weight range 7,820 (85%) (6)

Target population for treatment with omalizumab 7,820

Proposed number of patients to receive omalizumab 1,564 (20%) (7)

C: Estimated usage (volume)

Proposed omalizumab regimens
375 mg 2x every 4 weeks 7.5% (8)
300 mg 2x every 4 weeks 15.1% (8)
225 mg 2x every 4 weeks 20.4% (8)
300 mg 1x every 4 weeks 25.8% (8)
150 mg 1x every 4 weeks 31.2% (8)

Treatment length
- 52 weeks for patients responding to omalizumab treatment (see box)

Total volume of omalizumab (assuming all patients are responders) 7.37x10^6 mg

WHO DDD 16 mg (9)
Total DDD 4.61x10^5

D: 2011

Proposed number of patients to receive omalizumab 1,485

Total volume of omalizumab (assuming all patients are responders) 7.0x10^6 mg
WHO DDD           16 mg (9)
Total DDD         $4.38 \times 10^5$

The estimated eligible number of patients for this drug is small. Therefore, it is important to consider that the results of the comparative analysis are particularly sensitive to any uncertainties in the estimate. In these cases a small variation in the number of estimated patients will have a large impact on the ratio to actual usage. Figures pertaining to small treatment populations must be treated with caution.

References

1. The number of patients admitted to hospital two or more times for asthma in a 12 month period has been calculated using Hospital Episode Statistics (HES) data, by using an anonymous patient identifier to isolate those individuals that have been admitted to A&E on two occasions in the past year. Source: NICE TA133 costing template.

2. Estimating the national number of patients that have had three or more severe exacerbations of asthma within a 12 month period - at least one of which required admission to hospital, and a further two of which required treatment or monitoring in excess of the patient’s usual regimen - in an accident and emergency unit is difficult and subject to a significant uncertainty. HES data does not record attendances at an A&E department, only those attendances that are admitted to the hospital. HES data was used to identify the patient population that had been admitted to hospital once in the past 12 months for asthma calculated as being 41,587 individuals. Source: NICE TA133 costing template.

3. A national census of those attending UK accident and emergency departments with asthma. Partridge MR, Latouche D, Trako E et al. (1997) Journal of Accident and Emergency Medicine 14: 16-20. The census undertaken in 1994 reported that 24.5% of those attending A&E had attended A&E within the previous 3 months. These data have been used as a proxy to identify the proportion of patients that were admitted to hospital once and attended A&E on at least two occasions.


5. The proportion of patients with immunoglobulin E (IgE) levels in the required range has been estimated using data supplied in the manufacturer’s model.

6. The proportion of patients with weight in the target range to receive treatment has been estimated using data supplied in the manufacturer's model.

7. Uptake of omalizumab has been estimated following expert opinion. The guidance is very specific in the population that omalizumab is recommended for: the patient should have documented compliance with inhaled high-dose corticosteroids and long acting beta2 agonists, in addition to leukotriene receptor agonists, theophyllines, oral corticosteroids and beta2 agonist tablets and smoking cessation where clinically appropriate. Source: NICE TA133 costing template.
8. The proposed omalizumab regimens have been taken from clinical trial data. Source: Xolair cost schedule - manufacturer’s submission to NICE.

9. WHO DDD is obtained from WHO website: http://www.whocc.no/atc_ddd_index/?code=B01AC04

Observed uptake

Use in primary care is very low and so only data form the IMS Health HPAI data has been used.

Results

The table below shows expected and observed use and the ratio between them for 2010 and 2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (DDDs)</th>
<th>Observed (DDDs)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>461,000</td>
<td>334,884</td>
<td>0.73</td>
</tr>
<tr>
<td>2011</td>
<td>475,000</td>
<td>439,204</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Since the number of patients per SHA is low a sub-national analysis is not appropriate.

Issue

Omalizumab is a long-term treatment that has been available in the UK since October 2005 and has been NICE approved since November 2007. Therefore, over time, the number of responder patients on treatment has gradually increased. Given the lack of evidence for establishing the number of non-responders and the assumption that this would be a small fraction of those treated, all patients were assumed to respond to treatment in this estimate.

Consultation questions

1. Are there alternative sources of data representative of clinical practice, which would allow an exploration of the number of patients who respond to treatment vs. non responders?
Peginterferon Alfa-2a and 2b for hepatitis C

A: Summary

NICE have issued three appraisals of peginterferon alfa for use in hepatitis C, namely TA75 which covers moderate to severe hepatitis C, TA106 which covers the treatment of mild chronic hepatitis C and TA200 which replaced parts of the guidance in TA75 and TA106.

NICE recommends peginterferon alfa (2a or 2b) plus ribavirin as a possible treatment for people with chronic hepatitis C:

- who have been treated previously with peginterferon alfa (2a or 2b) plus ribavirin, or with peginterferon alfa monotherapy, but their hepatitis C didn't improve, or improved but then got worse again or

- who also have an HIV infection.

NICE also recommends short courses of treatment with peginterferon alfa (2a or 2b) plus ribavirin for people whose hepatitis C has greatly improved within 4 weeks of starting treatment and who are suitable for short treatment courses. Whether a person is suitable for a short treatment course will depend on a number of factors.

B: Estimate of eligible patient

The model was developed by MSD with input from Roche, and submitted to NICE for review. MSD and Roche are the manufacturers of the two forms of peginterferon alfa available in England. The model and the expected volume use figures for 2010. The corresponding results for 2011 appear in part D.

Reference

<table>
<thead>
<tr>
<th>Number of patients diagnosed with chronic Hepatitis C</th>
<th>52,441</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients eligible for treatment</td>
<td>36,709 (70%)</td>
</tr>
<tr>
<td>Number of patients expected to participate in treatment with peginterferon</td>
<td>21,291 (58%)</td>
</tr>
</tbody>
</table>

C: Estimated usage (volume)

Reference

<table>
<thead>
<tr>
<th>Number of patients treated with peginterferon</th>
<th>21,291</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of daily doses assuming patients receiving treatment for 48 weeks in the year (genotypes 1 and 4, assumed to be 50% of patients)</td>
<td>3,576,888 (3,4)</td>
</tr>
<tr>
<td>Number of daily doses for patients receiving treatment for 24</td>
<td>1,788,360 (3,4)</td>
</tr>
</tbody>
</table>
weeks in the year (genotypes 2 and 3), assumed to be 50% of
patients)

Total volume (daily doses) 5,365,248

There are other genotypes and patients co-infected with HIV and, for some of these, longer
treatment may be appropriate but they are comparatively rare.

**D: For 2011**

Estimate of eligible patients

<table>
<thead>
<tr>
<th>Total number of patients</th>
<th>57,040</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated usage (volume)</td>
<td></td>
</tr>
<tr>
<td>Total volume (daily doses)</td>
<td>5,835,876</td>
</tr>
</tbody>
</table>

**References:**

1. “Hepatitis in the UK”, HPA report 2009, figures for 2009 to 2011 are forecast from historic values.
2. TA200 costing template
4. “Hepatitis in the UK”, HPA report 2012, page 13, gives estimates of 45 per cent for each of genotypes 1 and 3 and with other genotypes constituting 10 per cent in England,

**Observed Uptake**

Usage data was provided by Roche and MSD as the companies believed that homecare use made the IMS Health HPAI data unsuitable. Roche provided their data as a number of weeks treatment where each pre-filled syringe or pen (135 mcg or 180 mcg) was regarded as one week’s treatment. This was converted to an equivalent number of days by multiplying by seven. MSD provided the number of pens by strength, which were converted to micrograms and then to an equivalent number of days using the WHO value of 7.5 mcg for the Defined Daily Dose.

Although the Roche product is licensed for both Hepatitis B and C, the company believe that use is almost entirely for Hepatitis C. The MSD product is only licensed for use in Hepatitis C.

**Results**

Given the uncertainties about some of the parameters in the model a comparison was made only at national level.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (Doses)</th>
<th>Observed (Doses)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>5,365,248</td>
<td>1,492,373</td>
<td>0.28</td>
</tr>
<tr>
<td>2011</td>
<td>5,835,876</td>
<td>1,393,855</td>
<td>0.24</td>
</tr>
</tbody>
</table>
Issues

We don’t know what proportion of treated patients have the different genotypes. This is important as it affects treatment length.

We don’t know how many but some people with chronic hepatitis C decide against treatment. There can be several reasons for this, for example if they:

• do not have any symptoms
• are willing to live with the risk of cirrhosis at a later date
• do not feel that the potential benefits of treatment outweigh the side effects that treatment can cause

We also don’t know how many patients from those who use drugs intravenously end up with re-infection.

We know diagnosis rates can vary.

Consultation questions

How can we obtain sub-national estimates by genotype? How can we obtain figures on informed dissent? Are there robust estimates of re-infection? How can diagnosis be improved?
Sunitinib for first line treatment of renal cell carcinoma and second line stromal gastrointestinal tumours

A: Summary
Sunitinib, a tyrosine kinase inhibitor, is licensed for the treatment of advanced or metastatic renal cell carcinoma (but see NICE Guidance, below). It is also licensed for the treatment of unresectable or metastatic malignant gastro-intestinal stromal tumours, after failure of imatinib, and for the treatment of unresectable or metastatic pancreatic neuroendocrine tumours (BNF 63)

Sunitinib is recommended:

- In NICE Technology Appraisal TA179 as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if:
  - imatinib treatment has failed because of resistance or intolerance, and
  - the drug cost of sunitinib (excluding any related costs) for the first treatment cycle will be met by the manufacturer.

- In NICE Technology Appraisal TA169 as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

It is not recommended for second line advanced/metastatic renal cell carcinoma and has not been licensed for the treatment of breast cancer.

B: Estimate of eligible patients

<table>
<thead>
<tr>
<th>Renal cell carcinoma</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of newly diagnosed kidney cancers</td>
<td>7,078 (90%) (1)</td>
</tr>
<tr>
<td>Total number of patients with renal cell carcinoma</td>
<td>6,370</td>
</tr>
<tr>
<td>a) From the total, patients with stage III (advanced) renal cell carcinoma</td>
<td>1,656 (26%) (3)</td>
</tr>
<tr>
<td>b) From the total, patients with stage IV (metastatic) renal cell carcinoma</td>
<td>1,083 (17%) (3)</td>
</tr>
<tr>
<td>c) From the total, patients with stage I and II renal cell carcinoma</td>
<td>3,631</td>
</tr>
<tr>
<td>d) Number of former stage I and II patients with recurrence</td>
<td>1,094 (33.3%) (4)</td>
</tr>
</tbody>
</table>
Total number of patients in the above groups (A+B+D) 3,948

Overall proportion of patients that present with an Eastern Cooperative Oncology Group performance status of 0 or 1 AND are suitable for immunotherapy 2,685 (68.0%) (5)

Total number of renal cell carcinoma patients eligible for treatment 2,685

Gastrointestinal carcinoma

Number of newly diagnosed GISTs 758 (6)

a) Proportion of GISTs that are metastatic and/or unresectable 152 (20%) (7)
b) GIST patients not in the above cohort 606 (80%) (7)
c) Proportion of GISTs that subsequently relapse at the metastatic and/or unresectable stage 121 (20%) (8)

Total number of people with metastatic and/or unresectable GISTs (A+C) 273

Patients unable to tolerate imatinib 14 (5%) (9)

Patients in whom imatinib fails 191 (70%) (9)

Total number of patients eligible for sunitinib treatment 205

Total number of patients (renal cell and gastrointestinal carcinomas combined) 2,890

C: Estimated usage (volume)

Renal cell carcinoma

Patients who receive first cycle of sunitinib 2,685

Patients who do not respond to first cycle of sunitinib or drop out after the first cycle due to adverse effects 349 (13%) (10)

Patients who receive further cycles of sunitinib 2,336

7.2 (10)
Further number of cycles of sunitinib received

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cycles</td>
<td>19,504</td>
</tr>
<tr>
<td>Average volume per cycle</td>
<td>1,013 mg (10)</td>
</tr>
<tr>
<td><strong>Total volume sunitinib for renal cell carcinoma</strong></td>
<td><strong>1.98x10^7 mg</strong></td>
</tr>
</tbody>
</table>

**Gastrointestinal carcinoma**

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who receive first cycle of sunitinib</td>
<td>205</td>
</tr>
<tr>
<td>Patients who do not respond to first cycle of sunitinib or drop out after the first cycle due to adverse effects</td>
<td>41 (20%) (11)</td>
</tr>
<tr>
<td>Patients who receive further cycles of sunitinib</td>
<td>164</td>
</tr>
<tr>
<td>Further number of cycles of sunitinib received</td>
<td>4     (11)</td>
</tr>
<tr>
<td>Total cycles (thousands)</td>
<td>861</td>
</tr>
<tr>
<td>Average volume per cycle</td>
<td>1,240 mg (12)</td>
</tr>
<tr>
<td><strong>Total volume sunitinib for renal cell carcinoma</strong></td>
<td><strong>1.07x10^6 mg</strong></td>
</tr>
</tbody>
</table>

**Total volume (renal cell and gastrointestinal carcinomas combined)** 2.08x10^7 mg

It is not anticipated that the estimated number of patients will be treated, or volume of medicine used, immediately following publication of guidance. It may, for example, be a period of time before patients present for treatment and this level is reached.

The estimated eligible number of patients for this drug is small. Therefore, it is important to consider that the results of the comparative analysis are particularly sensitive to any uncertainties in the estimate. In these cases a small variation in the number of estimated patients will have a large impact on the ratio to actual usage. Figures pertaining to small treatment populations must be treated with caution.

**D: For 2011**

**Estimate of eligible patients**

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients (renal cell and gastrointestinal carcinomas combined)</td>
<td>2,770</td>
</tr>
</tbody>
</table>

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Estimated usage (volume)
Total volume (renal cell and gastrointestinal carcinomas combined)  1.99x10^7 mg

References
3. Proportion of stage III and IV renal cell carcinomas at the time of initial diagnosis. Source: NICE TA169, section 2.3.
4. We assume patients with stage I and II disease at the time of diagnosis will go on to be eligible for first-line treatment with sunitinib due to recurrence, based on Cohen HT, McGovern FJ (2005), Renal-cell carcinoma, The New England Journal of Medicine, Vol. 353, No. 23 pp. 2477-90
5. We assume that if a patient presents with ECOG performance status of 0 or 1 then based on clinical opinion they would have been offered immunotherapy. 68% taken from patient characteristics in Elson P, Witte RS, Trump DL, (1988) Prognostic factors for survival in patients with recurrent or metastatic renal cell carcinoma, Cancer Research 48: 7310–3.
6. Assuming incidence of 15 per million. Source: NICE TA86 - Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours. A small minority of GISTs occurs in the paediatric population which is excluded from this TA, however this has been ignored for the purpose of costing.
9. See page 12 of the manufacturer’s submission for this TA, which states that 5% of patients are intolerant of imatinib and a further 70% of patients receiving the drug will develop resistance.
11. Based on mean progression-free survival data from manufacturer. Source: NICE TA169. Progression free survival (PFS) is 27.3 weeks, which equates to 5 cycles on average. The number of cycles has been rounded up as it is assumed that dispensed
medicines are not returned part used. Subtracting the initial cycle, there are further 4 cycles on average.

12. Based on manufacturer's assumption. BNF's recommended dosage is 50mg/once daily for four consecutive weeks with two weeks rest. Dose intensity is estimated at 88.6%, as per page 82 of the manufacturer's submission for this TA.

**Observed uptake**

Pfizer, the manufacturers of sunitinib, advised that the IMS Health hospital data would not be accurate and provided data directly to the HSCIC.

**Results**

The table below shows expected and observed use and the ratio between them for 2010 and 2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (mgs)</th>
<th>Observed (mgs)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>20,800,000</td>
<td>12,144,650</td>
<td>0.58</td>
</tr>
<tr>
<td>2011</td>
<td>19,900,000</td>
<td>11,455,149</td>
<td>0.58</td>
</tr>
</tbody>
</table>

The charts below compare the observed and expected use for 2010 and 2011 at SHA level.

![Ratio of observed to expected, sunitinib 2010 chart](chart_image)
The charts below compare the observed and expected use for 2010 and 2011 at Cancer Network level.
The chart below shows the net ingredient cost by quarter for England. Data is taken only from the IMS Health HPAI system which covers hospital use as primary use is very small (less than 1 per cent of the total). The manufacturer indicated that the data in the HPAI data was an underestimate.
**Issue**
This medicine has been placed in section 2 because there are significant uncertainties involved in establishing an estimate of the eligible patient population. For the Gastrointestinal carcinoma indication, small patient numbers are noted. The BNF gives a wide dosage range, from 25-75mg daily. More evidence of Sunitinib use in clinical practice, specifically around dosing and cycles, would enable a more robust estimate to be developed across both indications.

**Consultation questions**

1) What sources of evidence are available to establish a broad range of clinical practice with regard to cycle length, number and dosage across indications for this medicine?
2) What alternative therapies are available? How can we account for non-NICE appraised alternative medicines?
3) What proportions of patients decide not to have treatment?
Alzheimer’s Disease – donepezil, galantamine, rivastigmine, memantine

For 2010

A: Summary

Donepezil and galantamine are indicated in mild to moderate dementia in Alzheimer’s disease; rivastigmine in mild to moderate dementia in Alzheimer’s disease or in Parkinson’s disease and memantine in moderate to severe dementia in Alzheimer’s disease (BNF 61). NICE has appraised these drugs for the treatment of Alzheimer’s disease (NICE technology appraisal guidance 111, 2007):

- The three acetylcholinesterase inhibitors donepezil, galantamine and rivastigmine are recommended as options in the management of patients with Alzheimer’s disease of moderate severity only (that is, subject to section 1.2 below, those with a Mini Mental State Examination [MMSE] score of between 10 and 20 points), and under certain conditions (see guidance).
- Memantine is not recommended as a treatment option for patients with moderately severe to severe Alzheimer’s disease except as part of well-designed clinical studies.

This guidance was issued in November 2006 and was amended in September 2007 following the outcome of a judicial review in August 2007. The amendments clarified the steps healthcare professionals should take when assessing whether Alzheimer’s disease is of moderate severity. The guidance was reviewed and published in March 2011, and the later guidance forms the basis for the 2011 estimate contained in this report where memantine has been recommended.

B: Estimated eligible patients

<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females:</td>
<td>396,513</td>
</tr>
<tr>
<td>Males:</td>
<td>210,557</td>
</tr>
<tr>
<td>Subtotal</td>
<td>607,070</td>
</tr>
<tr>
<td>Estimated cases with mild AD (MMSE score 21–26)</td>
<td>182,121 (30%)</td>
</tr>
<tr>
<td>Estimated cases with moderate AD (MMSE score 10–20)</td>
<td>242,828 (40%)</td>
</tr>
</tbody>
</table>

QOF for 2009/10 gave a figure of 246,921 patients with a diagnosis of dementia (including Alzheimer’s disease). This would give an upper limit of the number of patients with moderate AD of 98,768.
Estimated cases with moderate AD 242,828 (3)

Patients initially prescribed treatment each year (for initial 6 months) 33,510 (13.80%) (4)

Patients continuing treatment for three years 23,122 (69%) (5)

Number of monthly treatments (over 15 months) once steady state has been reached 1,206,871 (6)

Number of daily doses (over 15 months once steady state reached) 36,688,882 (7)

Equivalent number of patients receiving a daily dose for a whole year at steady state: 80,458

Number of daily doses (thousands):
donepezil hydrochloride (60%) 22,013 (8)
Galantamine (21%) 7,705 (8)
Rivastigmine (19%) 6,971 (8)

C: Estimate of total volumes:

Donepezil hydrochloride 1.84x10^8 mg (9)
Galantamine 1.44x10^8 mg (9)
Rivastigmine 4.49x10^7 mg (9)

Using the APHO figures gives 36,688,882 doses, while using QOF prevalence figures as a starting point gives 14,258,538 daily doses.

It is not anticipated that the estimated number of patients will be treated, or volume of medicine used, immediately following publication of guidance. It may, for example, be a period of time before patients present for treatment and this level is reached.


References:


2. Estimate of proportion that have mild AD (as defined as scoring over 20 on the ‘Mini mental state examination’) based on expert opinion as there is very little data to quantify patients at different stage of disease. The appraisal and the clinical guideline on dementia care notes that cognitive assessment and interpretation of the score should take full account of other factors known to affect performance such as language fluency, learning disability or language problem. Our calculation of the proportion that are mild or moderate includes those assessed as mild / moderate using supplementary clinical assessment where appropriate.

3. Estimate of proportion that has moderate AD (as defined as scoring between 10 and 20 on the ‘Mini mental state examination’) based on expert opinion. The subtotal of patients with mild and moderate AD is therefore 70 per cent which is in line with figures reported in the assessment report produced for this appraisal (http://www.hta.ac.uk/fullmono/mon1001.pdf).

4. The latest guidance makes a distinction between mild and moderate patients, but there is very little evidence to estimate use in each group. Assuming that everyone eligible commences treatment is unrealistic. Comparing current spend on these drugs indicates 100 per cent compliance results in annual drug cost of £190 million. Initiation of treatment has been estimated on the assumption that twice as many patients with moderate disease are identified and commence treatment than patients with mild disease, and the total treatment cost is in line with what is known to be the annual spend. Source: NICE TA111.

5. The percentage of patients continuing treatment is based on audit data from Memory Clinics. This is considerably higher than that in trial patients and may be due to patients remaining on treatment inappropriately or a better response in the general population. Source: NICE TA111.

6. Assuming a constant rate of incidence at 13.8 per cent, and that 69 per cent of patients who start treatment continue to be treated for three years. Steady state is reached in year 3 from initial introduction of the drugs.

7. The number of monthly treatments multiplied by the mean month length of 30.4 days.

8. Estimated weighted use is based on usage data from PASA Pharmex system for period Jul/Aug/Sep 2006. Source: Costing template accompanying NICE TA111.

9. Dose per day based on volumes from PASA Pharmex system for period Jul/Aug/Sep 2006, incorporating varying dosage. Source: Costing template accompanying NICE TA111.
**Observed uptake**

These drugs are used in both primary and secondary care and so data from both versions of ePACT and IMS Health’s HPAI system were used. Primary care accounted for 66.9 per cent of total use (measured in DDDs) in 2010.

**Results**

The table below shows expected and observed use and the ratio between them for 2010.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (QOF)</th>
<th>Expected (Estimated prevalence)</th>
<th>Observed</th>
<th>Ratio (QOF)</th>
<th>Ratio (Estimated prevalence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>14,260,000</td>
<td>36,689,000</td>
<td>44,864,937</td>
<td>3.15</td>
<td>1.22</td>
</tr>
</tbody>
</table>

The charts below compare the observed and expected use for 2010 at SHA level.

**For 2011**

**A: Summary**

Donepezil and galantamine are indicated in mild to moderate dementia in Alzheimer’s disease; rivastigmine in mild to moderate dementia in Alzheimer’s disease or in Parkinson’s disease and memantine in moderate to severe dementia in Alzheimer’s disease (BNF 60).
NICE has reviewed the appraisal for these drugs for the treatment of Alzheimer’s disease (NICE technology appraisal guidance 217, 2011).

The review and re-appraisal of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer’s disease has resulted in a change in the guidance. Specifically:

- donepezil, galantamine and rivastigmine are now recommended as options for managing mild as well as moderate Alzheimer's disease, and
- memantine is now recommended as an option for managing moderate Alzheimer's disease for people who cannot take AChE inhibitors, and as an option for managing severe Alzheimer's disease

**B: Estimate of eligible patients**

<table>
<thead>
<tr>
<th>Estimated eligible patients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of dementia</td>
<td></td>
</tr>
<tr>
<td>Females: 428,485</td>
<td>(1)</td>
</tr>
<tr>
<td>Males: 304,724</td>
<td>(1)</td>
</tr>
<tr>
<td>Subtotal: 733,208</td>
<td></td>
</tr>
</tbody>
</table>

Proportion of people with dementia that have

- Alzheimer's disease: 62% (454,589) (2)
- Proportion diagnosed: 43% (195,019) (3)

Mild Alzheimer’s disease

- Estimated cases with mild AD (MMSE score 21–26) 108,040 (55.4%) (4)
- Proportion of people diagnosed with mild Alzheimer's disease who are referred to a specialist 75,628 (70%) (4)
- Proportion of people diagnosed with mild Alzheimer's who are referred to a specialist and have some form of treatment 68,950 (91.2%) (4)
- Proportion of treated people with mild Alzheimer's disease taking AChE inhibitors 63,931 (92.7%) (4)
<table>
<thead>
<tr>
<th>Compliance with treatment</th>
<th>51,145 (80%)</th>
<th>(4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion treated with donepezil</td>
<td>35,136 (68.7%)</td>
<td>(5)</td>
</tr>
<tr>
<td>Proportion treated with galantamine</td>
<td>10,280 (20.1%)</td>
<td>(5)</td>
</tr>
<tr>
<td>Proportion treated with rivastigmine</td>
<td>5,728 (11.2%)</td>
<td>(5)</td>
</tr>
</tbody>
</table>

**Moderate Alzheimer’s disease**

| Proportion of people diagnosed with Alzheimer’s disease whose disease is moderate | 62,601 (32.1%) | (4) |
| Proportion of people diagnosed with moderate Alzheimer’s disease who are referred to a specialist | 53,211 (85%) | (4) |
| Proportion of people diagnosed with moderate Alzheimer’s disease referred to a specialist and have some form of treatment | 51,082 (96%) | (4) |
| Proportion of treated people with moderate Alzheimer’s disease taking AChE inhibitors or memantine | 49,550 (97%) | (4) |
| Compliance of people with Alzheimer’s that are diagnosed with moderate Alzheimer’s referred to a specialist treated with AChEIs or memantine | 39,640 (80%) | (4) |
| Proportion treated with memantine | 8,704 (21.96%) | (5) |
| Proportion treated with AChE inhibitors | 30,937 (78.4%) | (5) |
| Proportion treated with donepezil | 21,253 (68.7%) | (5) |
| Proportion treated with galantamine | 6,218 (20.1%) | (5) |
| Proportion treated with rivastigmine | 3,465 (11.2%) | (5) |

**Severe Alzheimer’s**

| Proportion of people diagnosed with Alzheimer’s disease whose disease is severe | 24,377 (12.5%) | (4) |
Proportion of people diagnosed with severe Alzheimer's disease who are referred to a specialist 17,308 (71%) (4)

Proportion of people diagnosed with severe Alzheimer's disease referred to a specialist and have some form of treatment 12,964 (74.9%) (4)

Proportion of treated people with severe Alzheimer's disease treated with memantine 5,365 (31%) (4)

Compliance of people with Alzheimer's that are diagnosed with severe Alzheimer's referred to a specialist treated with memantine 4,292 (80%) (4)

Total number of patients treated with:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>56,360</td>
</tr>
<tr>
<td>Galantamine</td>
<td>16,498</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>9,193</td>
</tr>
<tr>
<td>Memantine</td>
<td>12,996</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DDDs</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>7.5mg</td>
</tr>
<tr>
<td>Galantamine</td>
<td>16mg</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>9mg</td>
</tr>
<tr>
<td>Memantine</td>
<td>20mg</td>
</tr>
</tbody>
</table>

**C: Estimated usage (volume)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>1.54x10^8mg</td>
</tr>
<tr>
<td>Galantamine</td>
<td>9.64x10^7mg</td>
</tr>
</tbody>
</table>
**References:**


3. The manufacturer's submission of Pfizer suggested that 47.3% are formally diagnosed. Data from the Alzheimer's Society suggest that in 2007 there were 38.5% people with dementia register. Therefore the mean proportion 42.9% was used.

4. From manufacturer's submissions by manufacturers of donepezil and memantine (see NICE TA 217 and costing template http://guidance.nice.org.uk/TA217

5. Based on http://guidance.nice.org.uk/TA217 costing template

**Observed uptake**

Data from the HPAI and both ePACT systems was used since these drugs are used in all sectors. In 2011 (with memantine added to the list of positively appraised drugs) primary care accounted for 79.8 per cent.

Initiation packs of memantine have been counted as 28 DDDs as a pack is intended to be used over 28 days. This is higher than would be the result of using the physical quantity of drug.

**Results**

Since QOF data was not available for 2011/12 only the estimated prevalence was used.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (Estimated prevalence)</th>
<th>Observed</th>
<th>Ratio (Estimated prevalence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>33,500,000</td>
<td>49,504,256</td>
<td>1.48</td>
</tr>
</tbody>
</table>

The chart below shows the ratio between the observed and expected values at SHA level for 2011.
The charts below shows the net ingredient cost by quarter for England both including and excluding memantine. Data is taken from the PCA database (which covers both primary care and prescriptions issued in hospitals and dispensed in the community) and the IMS Health HPAI system which covers hospital use.
Cost Alzheimer’s drugs (including memantine)

Issues
These medicines appear in two costing templates; TA111 and TA217. These costing templates were developed separately and therefore it is not appropriate to compare the results from them in a time series. TA217 was launched in March 2011, and therefore the estimate here does not reflect a full year of implementation.

Questions

1. Is it appropriate to estimate patient numbers and usage where one drug in a TA does not have a full year of usage data?
2. Which is the more appropriate measure of prevalence?
Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia

A: Summary

Ezetimibe inhibits the intestinal absorption of cholesterol. It is licensed as an adjunct to dietary manipulation in patients with primary hypercholesterolaemia in combination with a statin or alone (if a statin is inappropriate), in patients with homozygous familial hypercholesterolaemia in combination with a statin, and in patients with homozygous familial sitosterolaemia (phytosterolaemia) (BNF 61)

Ezetimibe has been appraised by NICE for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (NICE technology appraisal guidance 132, 2007):

- **Ezetimibe monotherapy is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who would otherwise be initiated on statin therapy (as per NICE guidance TA 94 in adults with non-familial hypercholesterolaemia) but who are unable to do so because of contraindications to initial statin therapy.**

- **Ezetimibe monotherapy is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who are intolerant to statin therapy (as defined in section 1.6).**

- **Ezetimibe, coadministered with initial statin therapy, is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who have been initiated on statin therapy (as per NICE guidance TA 94 in adults with non-familial hypercholesterolaemia) when:**
  
  - serum total or low-density lipoprotein (LDL) cholesterol concentration is not appropriately controlled (as defined in section 1.5) either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy (as defined in section 1.6) and
  
  - consideration is being given to changing from initial statin therapy to an alternative statin.

- **When the decision has been made to treat with ezetimibe coadministered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost.**

- **For the purposes of this guidance, appropriate control of cholesterol concentrations should be based on individualised risk assessment in accordance with national guidance on the management of cardiovascular disease for the relevant populations.**
• **For the purposes of this guidance, intolerance to initial statin therapy should be defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised. Adverse effects include evidence of new-onset muscle pain (often associated with levels of muscle enzymes in the blood indicative of muscle damage), significant gastrointestinal disturbance or alterations of liver function tests.**

The guidance was published in November 2007 and it is recommended that it is read in conjunction with NICE guidance on the initiation of statin therapy (NICE technology appraisal guidance 94) and in the context of the following clinical guidelines also published by NICE:

- Type 2 Diabetes - newer agents (CG87)
- Secondary prevention in primary and secondary care for patients following a myocardial infarction (CG48)
- Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (CG67)
- Identification and management of familial hypercholesterolaemia (CG71)

**B: Estimate of eligible patients**

ONS mid-year population estimate (England) 2009 51,806,700 (1)

Remove patients with familial causes of hypercholesterolaemia, not explicitly mentioned in the guidance documents / covered by licence for ezetimibe:

- familial defective apo-B (FDB) 0.10% 51,807 (2)
- homozygous FH 0.0001% 52 (2)
- abnormalities of PCSK9 0.10% 51,807 (2)
- familial combined hyperlipidaemia (FCH) 0.50% 259,034 (2)
- type III hyperlipoproteinaemia 0.01% 5,181 (2)

Population of England, excluding patients with a form of primary hypercholesterolaemia not explicitly mentioned in the guidance document / covered by the licence: 51,438,821

Patients with a TC test record ≥ 5.0 mmol/l in 12 month period (patients with primary (familial or non-familial) hypercholesterolaemia) 6.94% 3,567,542 (3)

Proportion of patients receiving lipid-modifying treatment 31.99% 1,141,367 (3)

Proportion of patients switching statins or to combination therapy who could therefore be eligible for ezetimibe 30.0% 342,410 (4)
C: Estimated usage (volume)

ezetimibe daily dose (WHO DDD) 10 mg (5)

annual dose per patient 3650 mg

Total estimated volume $1.250 \times 10^9$ mg

The technology in this appraisal may not be the only treatment recommended in NICE guidance, or otherwise available in the NHS. Therefore, if a NICE technology appraisal recommends use of a technology, it is as an option for the treatment of a disease or condition. This means that the technology should be available for a patient who meets the clinical criteria set out in the guidance, subject to the clinical judgement of the treating clinician. The NHS must provide funding and resources (in line with the recommendations) when the clinician concludes and the patient agrees that the recommended technology is the most appropriate to use, based on a discussion of all available treatments.

D: 2011

Patients with a TC test record $\geq 5.0$ mmol/l in 12 month period (patients with primary (familial or non-familial) hypercholesterolaemia) 7.20% 3,701,577 (3)

Proportion of patients receiving lipid-modifying treatment 30.59% 1,132,161 (3)

Proportion of patients switching statins or to combination therapy who could therefore be eligible for ezetimibe 30.0% 339,648 (4)

Total estimated volume $1.240 \times 10^9$ mg

This estimate represents a significant increase on the eligible patient numbers calculated in the 2009 report. In part, this is to be expected as lipid level testing has become more commonplace. In addition, the template used in this report has been modified extensively from the estimate presented in the report covering 2009. This is because there was more up to date information available than had been used in the previous estimate.

References

1. ONS Mid-2009 Population Estimates: England; estimated resident population by single year of age and sex

3. IMS Disease Analyser, MAT December 2010


5. WHO ATC/DDD index available at http://www.whocc.no/atc_ddd_index/

**Observed uptake**

Use is overwhelmingly in primary care (99% of DDDs) but figures have been summed from both versions of ePACT and the IMS Health hospital system.

**Results**

The table below shows expected and observed use and the ratio between them for 2010 and 2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (DDDs)</th>
<th>Observed (DDDs)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>125,000,000</td>
<td>89,683,831</td>
<td>0.72</td>
</tr>
<tr>
<td>2011</td>
<td>124,000,000</td>
<td>81,705,958</td>
<td>0.66</td>
</tr>
</tbody>
</table>

NICE have revised their estimates from the previous report where expected use was estimated as 79.2 million doses.

The charts below compare the observed and expected use for 2010 and 2011 at SHA level.
The chart below shows the number of DDDs of ezetimibe taken from the PCA database.
Issue
This medicine has been placed in section 2 because there are significant uncertainties involved in establishing an estimate of the eligible patient population. For the cohort of patients considered here with a TC ≥ 5.0 mmol/l, there is a significant proportion that does not appear to receive any lipid modification therapy. Because of current data limitations it is not possible to identify the reasons why these patients do not have a record of drug treatment, and therefore make any judgements as to which therapy these patients would be eligible for (if any).

Consultation questions

1) Are there alternative sources of data which would allow an exploration as to the reasons why some patients do not receive lipid modification therapy, despite having a TC ≥ 5.0 mmol/l?

2) Of those patients who switch therapies, is it possible to estimate the proportions that should switch to combination therapy, ezetimibe monotherapy, or another statin?
Erlotinib

A: Summary

Erlotinib, a tyrosine kinase inhibitor, is licensed in combination with gemcitabine for the treatment of metastatic pancreatic cancer. It is also licensed for the treatment of locally advanced or metastatic non-small cell lung cancer after failure of previous chemotherapy and as monotherapy for maintenance treatment of locally advanced or metastatic non-small cell lung cancer with stable disease after four cycles of platinum-based chemotherapy (BNF 63).

Erlotinib has been appraised by NICE for non-small cell lung cancer (NICE technology appraisal guidance 162, 2008):

_Summary:

Erlotinib is recommended, within its licensed indication, as an alternative to docetaxel as a second-line treatment option for patients with non-small-cell lung cancer (NSCLC) only on the basis that it is provided by the manufacturer at an overall treatment cost (including administration, adverse events and monitoring costs) equal to that of docetaxel.

_Erlotinib is not recommended for the second-line treatment of locally advanced or metastatic NSCLC in patients for whom docetaxel is unsuitable (that is, where there is intolerance of or contraindications to docetaxel) or for third-line treatment after docetaxel therapy._

Although NICE has not appraised erlotinib for the treatment of pancreatic cancer, Roche have suggested that usage of erlotinib for pancreatic cancer is minimal and therefore does not affect the results of this report.

B: Estimate of eligible patients

NICE TA 162 recommends erlotinib as an alternative to docetaxel, for second line treatment of advanced/metastatic NSCLC if treatment costs are equal. Note that the NICE appraisal for docetaxel and erlotinib does not indicate the proportional split between these two therapies. Therefore the following calculations are based on the assumption that every patient identified in the 2nd line therapy group is treated with erlotinib without consideration of docetaxel. This means the estimated use will be above the observed usage, and therefore any comparison with observed usage will suggest underuse of erlotinib.

Lung cancer incidence (crude rates per 100,000 population)

- Men (71.6/100,000) 18,517 (1,2)
- Women (52.3/100,000) 14,633 (1,2)
Total incidence 33,150

Of which non-small cell lung cancer 28,012 (84.5%) (3)

(A) NSCLC patients not receiving surgery 24,174 (86.3%) (4)
NSCLC patients receiving surgery 3,838 (13.7%) (4)
(B) Surgical patients progressing 1,535 (40%) \( \text{(5)} \)

Total stage IIIb or IV NSCLC patients \( (A+B) \) 25,709
Receiving 1st line treatment 21,082 (82%) \( \text{(6)} \)
First line patients going to 2nd line chemotherapy 9,908 (47%) \( \text{(6)} \)

This estimate presents a significant increase over the 2009 report. The largest parameter change is in the number of patients going to 2nd line chemotherapy; which has risen from 33% in 2009 to 47% in 2010/11 according to a report commissioned by the manufacturer.

C: Estimated usage (volume)

Average volume per patient (per 125 day course) 17,645 mg \( \text{(7,8)} \)

Total estimated volume in 2nd line therapy (avg volume per patient (per 125 day course) x number of patients going to 2nd line therapy) \( 1.75 \times 10^8 \) mg

The technology in this appraisal may not be the only treatment recommended in NICE guidance, or otherwise available in the NHS. Therefore, if a NICE technology appraisal recommends use of a technology, it is as an option for the treatment of a disease or condition. This means that the technology should be available for a patient who meets the clinical criteria set out in the guidance, subject to the clinical judgement of the treating clinician. The NHS must provide funding and resources (in line with the recommendations) when the clinician concludes and the patient agrees that the recommended technology is the most appropriate to use, based on a discussion of all available treatments.

D: For 2011

Estimate of eligible patients:

Estimated usage (volume): \( 1.78 \times 10^8 \) mg

References


6. The number of patients going from first line to second line chemotherapy. Kantar Health Patient Case Record study (2011). Data provided by the manufacturer.

7. Average length of erlotinib treatment is 125 days. Erlotinib for the treatment of NSCLC NICE Technology Appraisal 2008; TA162 p5.

8. Average dose per day (141.2 mg) taken from calculations supplied by the manufacturer based on pack sales data.

**Observed uptake**

This drug is used primarily in secondary care but the manufacturer (Roche) felt that the data collected by IMS Health was incomplete, partly because of homecare use and partly because of problems collecting data where aseptic units were involved. They therefore provided their own usage data for this analysis.

**Results**

The table below shows expected and observed use (data from Roche) and the ratio between them for 2010 and 2011 using the expected number of patients. However these figures do not take account of patients treated with docetaxel. It is not possible to do a combined analysis of erlotinib and docetaxel as docetaxel has a wider range of indications.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (mg)</th>
<th>Observed (mg)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>175,000,000</td>
<td>42,802,661</td>
<td>0.24</td>
</tr>
<tr>
<td>2011</td>
<td>178,000,000</td>
<td>43,695,918</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Note that NICE have revised their estimates since the last report which used an expected annual use of 37,800,000 milligrams.

Erlotinib is used almost entirely in the secondary care sector. The chart below shows the estimated spend on erlotinib in hospitals using data from the IMS Health HPAI system. As noted above, this may be an underestimate due to missing homecare data.
Issues

This estimate is based on the assumption that every patient identified in the 2nd line therapy group is treated with erlotinib. However, as noted above, docetaxel is also a treatment option for this patient population which means the estimated use will be above the observed usage, and therefore any comparison with observed usage will suggest underuse of erlotinib.

Questions

1. How can we compare expected and observed usage for a medicine when it is an option for treatment and alternative medicines exist?

2. How can we better understand the number of patients who progress from 1st to 2nd line chemotherapy regimens? What publicly available data is available to support this?
Alitretinoin

A: Summary

Alitretinoin is indicated in severe chronic hand eczema refractory to potent topical corticosteroids (BNF 63).

Alitretinoin has been appraised by NICE for the treatment of severe chronic hand eczema (NICE technology appraisal guidance 177, 2009):

- **Alitretinoin is recommended, within its licensed indication, as a treatment option for adults with severe chronic hand eczema that has not responded to potent topical corticosteroids if the person has:**
  - severe disease, as defined by the physician’s global assessment (PGA) and
  - a dermatology life quality index (DLQI) score of 15 or more.

- **Alitretinoin treatment should be stopped:**
  - as soon as an adequate response (hands clear or almost clear) has been achieved or
  - if the eczema remains severe (as defined by the PGA) at 12 weeks or
  - if an adequate response (hands clear or almost clear) has not been achieved by 24 weeks.

B: Estimate of eligible patients

Patient pathways were sourced from the costing template accompanying TA177.

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population aged 18 years and older</td>
<td>40,797,400</td>
<td>(1)</td>
</tr>
<tr>
<td>Prevalence of hand eczema</td>
<td>4,079,740</td>
<td>(10%)</td>
</tr>
<tr>
<td>Number of severe chronic hand eczema cases</td>
<td>244,784</td>
<td>(6%)</td>
</tr>
<tr>
<td>Cases refractory to topical treatments</td>
<td>122,392</td>
<td>(50%)</td>
</tr>
<tr>
<td><strong>Estimated proportion that will be treated having not responded to topical corticosteroids</strong></td>
<td>30,598</td>
<td>(25%)</td>
</tr>
</tbody>
</table>

Of the population identified above, a proportion will receive alitretinoin therapy. Other patients will receive one of several other possible therapies for example; PUVA, cyclosporine or azathripine (which both also have indications as anti organ rejection agents). It is not possible to ascertain what proportion of patients will receive each of these therapies, or indeed whether any patients will switch treatments. For this reason, it has not been possible to produce a full estimate of the eligible patient population.

References

1) ONS Mid-2009 Population Estimates: England; estimated resident population by single year of age and sex. Males and females aged 18 years and older.

3) Expert opinion taken from the manufacturer’s submission.

**Observed uptake**

This drug is used both within primary and secondary care therefore data was taken from the two versions of ePACT and the HPAI database. Secondary care accounted for 80.8 per cent of use in 2011 (measured in DDDs).

**Results**

Since there is no clear basis on which to decide the proportion of eligible patients who should receive alitretinoin rather than alternative treatments, it is not possible to produce an estimate which could be compared with observed usage.

The chart below shows the net ingredient cost by quarter for England. Data is taken from the PCA database (which covers both primary care and prescriptions issued in hospitals and dispensed in the community) and the IMS Health HPAI system which covers hospital use.
Issue
Of the population identified above, a proportion will receive alitretinoin therapy. Other patients will receive one of several other possible therapies for example; PUVA, cyclosporine or azathioprine (which both also have indications as anti organ rejection agents). PUVA involves the application of a cream and exposure to UV light.

Questions

1. How can we account for the use of alternative (non-appraised) medicines in this estimate?

2. Is it appropriate use the apportioning of patients to alitretinoin and alternative medicines detailed in the costing template (which were developed to assess the financial impact of implementation at the time of the TA)?
Biologic drugs for Rheumatoid Arthritis (infliximab, rituximab, etanercept, adalimumab, abatacept, certolizumab, tocilizumab and golimumab)

A: Summary
A class of medicines excluded from previous reports were the biologic medicines used for a range of auto-immune conditions including rheumatoid arthritis (RA). These medicines, which include those known as anti-TNFs, share the property that they inhibit the tumour necrosis factor present in the body which promotes the inflammatory response. The inflammatory response causes many of the clinical problems associated with auto-immune disorders such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and psoriasis.

These medicines are important for the NHS as they represent a significant share of total expenditure on medicines (approximately 4 per cent of total expenditure on medicines in England in 2010 based on the figures in the HSCIC report, “Hospital Prescribing, England: 2010”). These medicines had not been included in previous reports for a number of reasons:
- most have multiple indications
- there are often alternative medicines for the same indication
- several are known to be distributed through the homecare supply route, so the usage data available to the HSCIC is considered to be incomplete.

This section presents a proposed approach to analysing the use of this group of medicines. We would welcome comments on the suitability of this method and ways in which it might be improved.

In November 2011, companies with anti-TNF medicines and other biologics medicines used in rheumatoid arthritis created a working group to explore the methodological and data issues with a view to gaining their inclusion in the report. An early decision was taken to concentrate on the rheumatoid arthritis (RA) indication. RA is the only indication in common for all biologics medicines and the indication with the greatest share of patients receiving biologics medicines. To enable a thorough review of the uptake of positively appraised medicines by NICE, the scope of the analysis included these medicines: abatacept, adalimumab, certolizumab, etanercept, golimumab infliximab, rituximab, and tocilizumab.

B: Estimate of eligible patients
There have been several technology appraisals for the use of biologics for active RA. These are:
- TA130 - Rheumatoid arthritis - adalimumab, etanercept and infliximab
- TA186 - Rheumatoid arthritis - certolizumab pegol
- TA195 - Rheumatoid arthritis - drugs for treatment after failure of a TNF inhibitor
- TA198 - Rheumatoid arthritis – tocilizumab
- TA225 - Rheumatoid arthritis (after the failure of previous anti-rheumatic drugs) – golimumab
- TA234 - Rheumatoid arthritis - abatacept (2nd line)
• TA247 Rheumatoid arthritis - tocilizumab (rapid review TA198) (Note this appraisal was published in February 2012 and outside the scope of the analysis)

The net effect of these multiple assessments has been to create a complex clinical pathway. To aid understanding NICE have produced an algorithm showing the clinical pathway for these medicines which can be accessed at

http://www.nice.org.uk/usingguidance/commissioningguides/biologicaltherapies/home.jsp?domedia=1&mid=A7446F31-19B9-E0B5-D426584413B64AB3

Note that this algorithm estimates that all patients who are eligible for treatment with a biologic will be receiving it either as monotherapy or with methotrexate. The clinical pathway was simplified to two dimensions: measuring the number of patients in England with RA (prevalence) and, of these, the proportion who would be eligible for treatment with a biologic in accordance with NICE recommendations.

To establish a population estimate for RA for England the IMS Health Disease Analyzer database was interrogated. The Disease Analyzer is a database of patient records from general practices in the UK. The extraction was based on data from 101 practices with a base population of 892,000 patients. To inform the query a set of relevant READ codes were used to cover the scope of all patients with RA. The list of READ codes was compiled by NICE after consulting with a number of rheumatologists. This list is available on request from the HSCIC.

This gives an estimated prevalence of 0.642 per cent. Applying this to the England population in 2011 (52,655,000 according to ONS 2010-based population estimates) gives an estimate of 338,000 patients where RA is in the patient record as a “problem” (i.e. diagnosis).

Three NHS centres specialising in the treatment of RA and who had maintained information systems monitoring patient characteristics were consulted. From their responses, and with the inclusion of evidence used to generate the original estimate used in the costing template for “TA195 Rheumatoid arthritis - drugs for treatment after failure of a TNF inhibitor” it was agreed that the average share of patients meeting the eligibility criteria, adjusted for tertiary referrals, was 15 per cent.

Multiplying the estimated prevalence by the proportion of patients with RA eligible for treatment with a biologic in accordance with NICE guidance produced a figure of 50,707 patients (15 per cent of 338,000)

**Estimate of Volume**

Elsewhere in this report the approach has been to convert the estimate of the number of eligible patients to an expected volume of medicine and then compare this with the observed volume of usage. Since the number of patients treated was known for one of these medicines, it was decided to convert observed medicine use to an estimated number of
treated patients which could then be added to the known number of patients treated. Figures on drug volume or of the number of patients treated were supplied by the manufacturing companies.

For certozilumab, the company was aware of the number of patients treated because of the Patient Access Scheme they operate. For the drugs infliximab, golimumab and adalimumab the companies used their own data to produce estimates of the numbers of patients treated. For rituximab, tocilizumab and etanercept companies provided data on sales and advice on the likely average dose. For abatacept the company did not provide any data but advised that the IMS HPAI data was adequate and provided assistance in producing an average dose.

For medicines with multiple indications, the usage associated with RA was determined by the companies through a variety of mechanisms including intelligence gathered through commercial data sources, company generated market intelligence and networks of representatives.

Note that rituximab and tocilizumab are normally used after the failure of anti-TNF medicines. The use of tocilizumab as appraised in TA247 is outside the remit of this work as the appraisal was only published in 2012.

The average annual doses used in the estimation of the number of patients used are shown in the table below. These dose assumptions are based on standard clinical practice for 2011 and are in accordance with the product licence for that indication. Some manufacturers made assumptions about the proportion of their product used for RA. They regard this information as commercially sensitive and were unwilling to release it.

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Assumed average annual dose (mg) and any other relevant assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>14 doses of 750 mg each, total of 10,500 mg</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Data from the British Society for Rheumatology Biologics Register was used to assess how many vials were likely to be used for different weight ranges to derive an average infusion dose of 264 mg and assumption of 7 infusions per annum per patient gives an annual average dose of 1,845 mg.</td>
</tr>
<tr>
<td>Golimumab</td>
<td>50 mg once per month giving annual total of 600 mg (company can distinguish use for RA from other uses)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Annual dosage assumed to be 40 mg every other week giving annual total of 1,040 mg</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Annual total of 2,392 mg. The company warn that this is only their best estimate but that there are many factors involved and so there is some uncertainty about this value.</td>
</tr>
<tr>
<td>Rituximab</td>
<td>The estimate for annual usage (based on 2 g at intervals of 8.7 months and compliance rate of 83 percent) is 2,290 mg</td>
</tr>
</tbody>
</table>
Toclizumab | Annual total of 5.88 g (based on assumed average dose of 8 mg/kg and assumed average weight of patients of 70 kg and 21 doses over 2 years)
---|---
Certozilumab | As patient numbers were supplied directly no assumptions concerning average dose were required

For some medicines, the dose is determined by bodyweight, and an average bodyweight of 70 kg for patients was used, as per the NICE assessment “Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor, Part review of NICE technology appraisal guidance 36, Review of NICE technology appraisal guidance 126 and 141 “.

There is considerable uncertainty in both the proportions of usage for the treatment of RA and the average/body weight doses for the medicines detailed above. Some companies are able to separate usage according to indication, whereas other companies have provided an estimate of usage in RA. The extent to which these uncertainties and assumptions used will impact on the final comparison of observed versus expected usage is likely to be significant.

**Results**

Estimates by strategic health authority have not been calculated as usage data is available at England level only. This is because provision of usage data (inclusive of the homecare supply route) below national level has not been possible for all companies.

One company could only provide data for 2011 and so the comparison has only been done for 2011.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (patients)</th>
<th>Observed (Patients)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>50,707</td>
<td>50,364</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Issues

This analysis has focused on the use of these medicines in RA. Several areas of uncertainty should be noted, which includes factors such as:

- Most of these medicines have multiple indications
- There are alternative medicine choices
- Uncertainties in determining the eligible patient population for a given year (incident vs. prevalent patients).
- The usage data has been derived from estimates of varying degrees of certainty. Thus, the comparison is not between an expected and observed value, rather a comparison of estimated usage against an estimate of actual usage. This could introduce significant variability in the results presented. Typically this degree of variance in a key parameter would be approached with a sensitivity analysis.
- Treatment failures and patients who withdraw from or decline treatment have not been accounted for in either the expected or observed data. This could potentially have a significant impact on the numbers of patients presented here.

Consultation questions

1. How appropriate is this approach? How can it be improved?

2. This analysis has only considered the use of these biologic medicines for their indication in RA. Is it possible to apportion usage to the other indications?

3. What data would be suitable for this purpose?

4. How could the numbers of patients who withdraw from or decline treatment/or where treatment fails be estimated?

5. How can the known gaps in utilisation data be reduced?
Future Developments

This report has attempted to address issues identified in previous editions of this publication, particularly around improved ways to develop estimates of eligible patients and to enhance the drug utilisation information by using additional sources, including the pharmaceutical industry. These would ensure that the selection of medicines to be reviewed was not unnecessarily restricted by gaps in the available data. Although progress has been made, these issues are complex to resolve and further work is required.

The Metrics Oversight Group is committed to continuing improvements in data collection and reporting at both national and sub-national levels.

Issues to be considered for future reports include:

- The re-organisation of the NHS which will be in place from April 2013
- Developments in the provision and recording of homecare data
- The potential of new sources of information, for example the Systemic Anti-Cancer Therapy (SACT) data set

This report has experimental status, and feedback from users is welcomed to help improve data collection and reporting. If you wish to comment, please use the associated feedback form. This includes some questions, but also requests general comments and suggestions.
Glossary

Technology Appraisal
A process used by NICE to assess the clinical and cost effectiveness of new and existing medicines and treatments and other interventions, and to provide guidance on their use by the NHS.

Clinical Guideline
A document produced by NICE containing recommendations, based on the best available evidence, on the appropriate treatment and care of people with specific diseases and conditions.

ePACT
A system provided by Prescription Services (part of the NHS Business Services Authority) to allow access to prescribing data. There are two versions, one for primary care and one for prescriptions written in secondary care but dispensed in the community.

HPAI
Hospital Pharmacy Audit Index, a database owned and maintained by IMS Health which contains data on use of medicines within hospitals based on issues from hospital pharmacies. Although it does not have complete coverage, it does hold data from the vast majority of hospitals in England.

PCA
Prescription Cost Analysis. In the context of this report, this refers to a database containing data on prescriptions dispensed in England maintained by the Health and Social Care Information Centre using data downloaded from Prescription Services (part of the NHS Business Services Authority).

PCT
Primary Care Trust

SHA
Strategic Health Authority

CN
Cancer Network

NATCANSAT
The National Cancer Service Analysis Team (NATCANSAT) which was established in 1996.
Appendix A: Selection of medicines and reason for exclusion

The table below shows the medicines that were considered for inclusion by the Metrics Expert Group and excluded, with the principal reason for that exclusion. This appendix only contains those medicines which were excluded after being selected for initial inclusion in the report. It does not include those medicines excluded by the sieving criteria used at the beginning of the medicines selection process. For many of these medicines, multiple exclusion criteria apply (alternative drugs, aseptic units, non-appraised indications etc.), and some case study examples have been used to highlight these more complex circumstances.

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Therapy area</th>
<th>Principal reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe</td>
<td>Lipid regulating</td>
<td>NICE and the company were unable to agree on a model for producing the estimates</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Osteoarthritis, COX2 inhibitors</td>
<td>Safety concerns about Cox II inhibitors since appraisal; anecdotal evidence of switch to standard NSAID with PPI</td>
</tr>
<tr>
<td>Etodolac</td>
<td>Osteoarthritis, COX2 inhibitors</td>
<td>Safety concerns about Cox II inhibitors since appraisal; anecdotal evidence of switch to standard NSAID with PPI</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>Osteoarthritis, COX2 inhibitors</td>
<td>Safety concerns about Cox II inhibitors since appraisal; anecdotal evidence of switch to standard NSAID with PPI</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>Psoriasis</td>
<td>Withdrawn from market</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Newer hypnotic drugs</td>
<td>Change in status of temazepam (to a controlled drug) would invalidate original estimates of use</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Newer hypnotic drugs</td>
<td>Change in status of temazepam (to a controlled drug) would invalidate original estimates of use</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>Newer hypnotic drugs</td>
<td>Change in status of temazepam (to a controlled drug) would invalidate original estimates of use</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>Obesity</td>
<td>Withdrawn from market</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>Obesity</td>
<td>Withdrawn from market</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Obesity</td>
<td>Other obesity medicines excluded</td>
</tr>
<tr>
<td>Drotrecogin alfa</td>
<td>Severe sepsis</td>
<td>Low usage</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Renal transplantation</td>
<td>Marketing authorisation removed in Europe at request of manufacturer in January 2009</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Renal transplantation</td>
<td>Substantial use in other indications and different treatment options available, so unable to determine volume</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Renal transplantation</td>
<td>Another medicine has substantial use in other indications and different treatment options available, so unable to determine volume</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Renal transplantation, severe eczema</td>
<td>Another medicine has substantial use in other indications and different treatment options available, so unable to determine volume</td>
</tr>
<tr>
<td>Medicine</td>
<td>Therapy area</td>
<td>Principal reason for exclusion</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------------------------------</td>
<td>-------------------------------------------------------------------</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>Prophylaxis of acute organ rejection in renal transplantation patients</td>
<td>Another medicine has substantial use in other indications and different treatment options available, so unable to determine volume</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Cancer: breast, lung</td>
<td>Aseptic unit</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Cancer: breast, pancreatic, lung</td>
<td>Homecare</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Cancer: breast, prostate, lung</td>
<td>Aseptic unit</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Cancer: colorectal</td>
<td>Aseptic unit</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Cancer: colorectal</td>
<td>Aseptic unit</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Cancer: leukaemia, gastro intestinal</td>
<td>Homecare</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Cancer: ovarian, breast, lung</td>
<td>Aseptic unit</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>Hepatitis B</td>
<td>Other Hepatitis B medicines excluded</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Hepatitis B</td>
<td>Homecare</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Hepatitis B</td>
<td>Homecare</td>
</tr>
<tr>
<td>Tenofovir disoproxil</td>
<td>Hepatitis B</td>
<td>Homecare</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Ms</td>
<td>Homecare</td>
</tr>
<tr>
<td>dabigatran etexilate</td>
<td>Venous thromboembolism</td>
<td>See expanded section</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Venous thromboembolism</td>
<td>See expanded section</td>
</tr>
<tr>
<td>Sertindole</td>
<td>Schizophrenia</td>
<td>Only available on a named patient basis</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Multiple myeloma</td>
<td>See expanded section</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Multiple myeloma</td>
<td>See expanded section</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Multiple myeloma</td>
<td>See expanded section</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Attention deficit hyperactivity disorder (ADHD)</td>
<td>See expanded section</td>
</tr>
<tr>
<td>Dexamfetamine</td>
<td>Attention deficit hyperactivity disorder (ADHD)</td>
<td>See expanded section</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Attention deficit hyperactivity disorder (ADHD)</td>
<td>See expanded section</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>Cancers of the blood</td>
<td>Can’t determine if 1st, 2nd etc</td>
</tr>
<tr>
<td>Nebulised therapy</td>
<td>Asthma</td>
<td>for children</td>
</tr>
<tr>
<td>Routine antenatal anti-D prophylaxis</td>
<td>Sensitisation in pregnancy</td>
<td>Couldn’t separate out use in pregnancy.</td>
</tr>
<tr>
<td>Dronedarone (2nd line)</td>
<td>Non-permanent atrial fibrillation</td>
<td>Safety concerns post guidance</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>Hyperparathyroidism (multiple forms)</td>
<td>Data not available by indication</td>
</tr>
</tbody>
</table>
Note on case study examples of excluded medicines

Some medicines which could not be included in section 1 or 2 of the report form interesting case study examples of the methodological challenges encountered. For this reason, a more detailed rationale for their exclusion is given below. NICE, companies and the HSCIC, ABPI and the OHE discussed potential methods for including these medicines, but, despite engagement from all parties, a solution could not be found. It is hoped that the notes below will stimulate wider discussion on how to resolve the methodological difficulties.

1. Anti-thrombolytics

**Rivaroxaban** is a direct inhibitor of activated factor X (factor Xa), and is given orally for prophylaxis of venous thromboembolism in adults after hip or knee replacement surgery.

**Dabigatran etexilate**, a direct thrombin inhibitor, is given orally for prophylaxis of venous thromboembolism in adults after total hip replacement or total knee replacement surgery. Dabigatran etexilate is also licensed for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and with at least one of the following risk factors: previous stroke, transient ischaemic attack, or systemic embolism, left ventricular ejection fraction <40%, symptomatic heart failure, age ≥75 years, or age ≥65 years in patients with diabetes, coronary artery disease, or hypertension.

NICE has recommended Rivaroxaban (TA 170) as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery.

NICE has recommended Dabigatran (TA 157) as a possible treatment to reduce the risk of venous thromboembolism in adults who have surgery to replace their hip or knee joint.

In 2012, both drugs were positively appraised by NICE as options for treatment in atrial fibrillation.

During the timeframe of this report, both Rivaroxaban and Dabigatran were options for prophylaxis of patients following hip and knee replacement surgery. However, low molecular weight heparin (LMWH) is widely used for this indication and does not have a NICE appraisal but is mentioned in CG92. LMWH is also used in numerous other indications. Fondaparinux is a synthetic pentasaccharide that inhibits activated factor X and is also used in thromboembolism prophylaxis. All of these medicines are valid ‘options’ for treatment. LMWH has wider usage than the indications of rivaroxaban and dabigatran, and no data exists to separate out its usage by indication. A comparative approach would certainly show overuse. It would therefore be potentially misleading to show variation in the use of these medicines.
2. ADHD Drugs

Methylphenidate and atomoxetine are used for the management of Attention Deficit Hyperactivity Disorder (ADHD); dexamfetamine is an alternative in children who do not respond to these drugs. Treatment of ADHD often needs to be continued into adolescence, and may need to be continued into adulthood. Currently none of the medications are licensed for initiation of treatment in adulthood.

Treatment with medication for ADHD (methylphenidate, atomoxetine and dexamfetamine), for children and adolescents, was appraised in TA98 and also features in a CG72 (Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults).

NICE CG72 assumes that prescribers will use the drug summary of product characteristics to inform their decisions for individual people. At the time of publication of the CG (September 2008), methylphenidate, atomoxetine and dexamfetamine did not have UK marketing authorisation for the treatment of adults with ADHD. However, atomoxetine is licensed for use in adults with ADHD when treatment with the drug began in childhood. Also, at that time, methylphenidate and atomoxetine did not have UK marketing authorisation for use in children younger than 6 years. There is considerable uncertainty about the number of adult patients who maintain their ADHD diagnosis from childhood or adolescence. Furthermore, usage data currently does not permit the differentiation of prescribing in primary care to children and adults thereby precluding an analysis of usage by age group and off-label use. However, this may be possible in the future, as newer data is expected to permit the analysis of prescribing to children and adults.

3. Multiple Myeloma

Lenalidomide, Bortezomib and Thalidomide

Lenalidomide is an immunomodulating drug with antineoplastic, anti-angiogenic, and pro-erythropoietic properties. It is licensed, in combination with dexamethasone, for the treatment of multiple myeloma in patients who have received at least one previous therapy.

TA171 states: *Lenalidomide (used together with dexamethasone) is recommended as a possible treatment for people with multiple myeloma who have already had at least two other treatments.*

Bortezomib, a proteasome inhibitor, is licensed as monotherapy for the treatment of multiple myeloma that has progressed despite the use of at least one therapy, and where the patient has already had, or is unable to have, bone-marrow transplantation. It is also licensed for use in combination with melphalan and prednisolone for the treatment of previously untreated multiple myeloma in patients who are not eligible for high-dose chemotherapy with bone marrow transplantation.
TA129 States: *Bortezomib monotherapy is an option for the treatment of progressive multiple myeloma in patients who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone-marrow transplantation, under the following circumstances:*

TA 228 states: *Bortezomib in combination with an alkylating drug and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if:*

- **high-dose chemotherapy with stem cell transplantation is considered inappropriate and**
- **the person is unable to tolerate or has contra-indications to thalidomide.**

**Thalidomide** was appraised by NICE in July 2011 (TA 228). NICE typically assumes that institutions will take three months to have finances in place to adopt guidance. In the case of thalidomide, uptake would thus respond to guidance around November 2011. In the initial selection of medicines for this report, it was decided that a medicine would not be included if there was less than one full year of usage data available for the period following appraisal. Thalidomide has been used for multiple myeloma treatment for many years prior to the appraisal, but it would not be appropriate to show variation with a denominator for the period over which Thalidomide was not positively appraised. This appraisal also extends the approval of bortezomib. If the earlier multiple myeloma appraisals were used as a basis for forming an estimate, then there is overlap between lenalidomide and bortezomib eligibility for those patients who cannot have a bone marrow transplant. Bortezomib also has a non-appraised use as first line therapy for multiple myeloma in combination with melphalan which is also licensed for regional arterial perfusion in localised malignant melanoma of the extremities and localised soft-tissue sarcoma of the extremities. It is because of these complexities that the decision was made to exclude these medicines from the analysis.
Appendix B: Cancer population methodology

To determine Cancer Network populations where estimate assumptions could be applied, the Metrics Expert Group liaised with NATCANSAT.

NATCANSAT supplied the Cancer Network population, using the methodology described below to estimate the catchment populations of provider units and Cancer Networks for use in the report.

The results are based on the agreed geographical boundaries of the Cancer Networks in England, cross tabulated with calculated catchment populations for the Radiotherapy Facilities in England using data taken from the Radiotherapy Data Set (RTDS). Like any data model, the accuracy of this approach is dependent on the quality of available data.

NATCANSAT have calculated Dominant Radiotherapy Provider Population Areas using the RTDS.

Data

The data extract used in this analysis.

- ONS 2009 mid year estimates for Census Ward populations.
- RTDS Data extract of unique patients taken for the time period April 2009-March 2011. The number of patients for each provider were summated for each Census Ward. These figures provided a percentage (market share) split for the ONS population data to be shared on a pro-rata basis. This methodology is NATCANSAT’s Method B calculation.
- The extract includes over 231,000 unique records.
- For a more detailed breakdown of the Method B methodology please visit http://www.natcansatmicrosite.net/microsite/rtds/

GIS Methodology

The UK is divided into approximately 10,000 Census Wards. Each Census Ward contains a population of approximately 5,000 people. Census wards in rural areas may cover a relatively large area but can contain a population of as few as 1,000 people. Conversely, Census Wards in urban areas may cover a relatively small area but can contain populations of up to 10,000 people.

A great deal of information is available (from the national census) on the demographic profile of the population contained in each Census Ward. Hospital patient episodes, cancer registry data and cancer mortality data can also be grouped by Census Ward.

Each Census Ward can therefore be regarded as a piece of a large data jigsaw, which when put together and analysed appropriately, can produce a data model of cancer services within the UK.

Mapping RTDS Data by Patient Post Code to Identify Dominant Radiotherapy Provider Population Areas

Each patient record in the RTDS extract taken contains the patient’s postcode. This postcode can then be geographically mapped to a Census Ward. The number of patients
from each Census Ward can then be summated by provider. These figures provide a percentage (market share) split for each Census Ward. Using this split NATCANSAT can distribute the ONS 2009 mid year estimate populations by all the providers that were used within a Census Ward. Thus the population of each Census ward is allocated on a pro-rata basis to one or more providers. The population allocated to each provider is then summated to arrive at a total catchment population for each trust.

**Estimating Catchment Populations for Tertiary Services**

Tertiary services tend to be provided within a large geographical area covering several Cancer units or even several Cancer Networks (e.g. Cardiothoracic Surgery, Neurological Surgery or Gynaecological Centre Surgery).

Cross boundary flows represent a relatively large percentage of a tertiary provider’s total workload (more than 90 per cent).

The frequency of tertiary surgical episodes may be so low that if an election style “first past the post” method is applied to the analysis of tertiary surgical services a provider often fails to ‘win’ a single Census Ward.

Therefore, utilising a “proportional representation” method is the most appropriate technique to estimate catchment areas and populations for providers of tertiary cancer services in the tertiary sector. Although the frequency of tertiary episodes is low, tertiary providers are allocated a proportion of each Census ward’s population that contains an episode on a pro-rata basis.\(^5\)

**Cancer Network population numbers**

These represent the mid-2009 estimates.

<table>
<thead>
<tr>
<th>Cancer Network</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anglia Cancer Network</td>
<td>2,851,046</td>
</tr>
<tr>
<td>Arden Cancer Network</td>
<td>1,091,217</td>
</tr>
<tr>
<td>Avon, Somerset &amp; Wiltshire Cancer Network</td>
<td>1,854,906</td>
</tr>
<tr>
<td>Central South Coast Cancer Network</td>
<td>1,903,863</td>
</tr>
<tr>
<td>Dorset Cancer Network</td>
<td>703,599</td>
</tr>
<tr>
<td>East Midlands Cancer Network</td>
<td>4,067,548</td>
</tr>
<tr>
<td>Essex Cancer Network</td>
<td>1,355,261</td>
</tr>
<tr>
<td>Greater Manchester &amp; Cheshire Cancer Network</td>
<td>3,207,316</td>
</tr>
<tr>
<td>Greater Midlands Cancer Network</td>
<td>1,888,749</td>
</tr>
<tr>
<td>Humber &amp; Yorkshire Coast Cancer Network</td>
<td>1,022,248</td>
</tr>
<tr>
<td>Kent &amp; Medway Cancer Network</td>
<td>1,748,166</td>
</tr>
<tr>
<td>Lancashire &amp; South Cumbria Cancer Network</td>
<td>1,436,745</td>
</tr>
<tr>
<td>Merseyside &amp; Cheshire Cancer Network</td>
<td>2,038,923</td>
</tr>
</tbody>
</table>

\(^5\) This method has been modified from a document prepared by Dr Brian Cottier in 2002, by Helen Forbes, NATCANSAT, 04/11/2010 (Updated April 2012)
<table>
<thead>
<tr>
<th>Cancer Network</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mount Vernon Cancer Network</td>
<td>1,951,578</td>
</tr>
<tr>
<td>North East London Cancer Network</td>
<td>1,647,093</td>
</tr>
<tr>
<td>North London Cancer Network</td>
<td>1,786,909</td>
</tr>
<tr>
<td>North Trent Cancer Network</td>
<td>1,757,596</td>
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<tr>
<td>North West London Cancer Network</td>
<td>1,178,700</td>
</tr>
<tr>
<td>Pan Birmingham Cancer Network</td>
<td>1,885,206</td>
</tr>
<tr>
<td>Peninsula Cancer Network</td>
<td>1,671,960</td>
</tr>
<tr>
<td>South East London Cancer Network</td>
<td>1,651,867</td>
</tr>
<tr>
<td>South West London Cancer Network</td>
<td>2,109,533</td>
</tr>
<tr>
<td>Surrey, West Sussex &amp; Hampshire Cancer Network</td>
<td>1,216,129</td>
</tr>
<tr>
<td>Sussex Cancer Network</td>
<td>925,326</td>
</tr>
<tr>
<td>Thames Valley Cancer Network</td>
<td>2,026,867</td>
</tr>
<tr>
<td>The North of England Cancer Network</td>
<td>3,046,281</td>
</tr>
<tr>
<td>Three Counties Cancer Network</td>
<td>1,026,452</td>
</tr>
<tr>
<td>Yorkshire Cancer Network</td>
<td>2,758,657</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>51,809,741</strong></td>
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</table>