Use of NICE appraised medicines in the NHS in England – 2012, experimental statistics
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This report may be of interest to members of the public and other stakeholders in helping them understand the use of NICE appraised medicines, locally and across England.

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Please note: on 7 February 2014 a revised version of this report was published to correct under reporting of the use of medicines for Alzheimer’s Disease, ADHD, Alitretinoin, Riluzole and exenatide and liraglutide. All other elements of the report are unaffected.
Use of NICE appraised medicines in the NHS in England – 2012, experimental statistics

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Executive Summary

This report, “Use of NICE appraised medicines in the NHS in England – 2012, experimental statistics” is the fourth review of the use by the National Health Service (NHS) in England of medicines positively appraised by the National Institute for Health and Care Excellence (NICE). It is published following the 2009 Pharmaceutical Price Regulation Scheme (PPRS) agreement, which contains a commitment to publish these metrics on an annual basis.

This report shows NHS medicine use during 2012 and provides historical data, where appropriate to aid interpretation. All medicines positively appraised by NICE were considered for inclusion, though many were subsequently excluded because of significant difficulties with the calculation of predicted or observed use (see Appendix A). The data is reported using the new NHS structure.

Two methods have been used to analyse medicine usage. First, an estimate approach compares estimated predicted use with observed use. Second, a variation approach was used to show the use of the medicines over time and how this use varies between Area Teams (ATs) and Clinical Commissioning Groups (CCGs).

Key Facts

- NHS medicine use for 54 medicines relating to 47 technology appraisals (TAs), are included. Medicines are analysed in 28 groups of medicines, with each group including medicines used to treat similar indications.

- The estimate approach analysed 18 medicines in 10 groups (see table 1 and section 3). Where a comparison could be made, observed use by the NHS in England was higher than the predicted use for two groups, lower for three, and around the expected level for three groups. For ranibizumab use was lower when it was assumed that one vial is used per eye, but around the expected level when it was assumed that one vial is used per patient, for both eyes. This report was unable to calculate a ratio for hepatitis C medicines.

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.

Table 1  Expected and observed use of NICE appraised medicines in 2012

<table>
<thead>
<tr>
<th>Technology</th>
<th>Ratio between expected use and observed use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease - donepezil, galantamine, rivastigmine, memantine</td>
<td>1.55</td>
</tr>
<tr>
<td>Carmustine implants</td>
<td>0.84</td>
</tr>
<tr>
<td>Diabetes (type 2) - exenatide and liraglutide</td>
<td>0.97</td>
</tr>
<tr>
<td>Diabetes (type 1 and type 2) - insulin glargine and insulin detemir</td>
<td>1.03</td>
</tr>
<tr>
<td>Hepatitis C – peginterferon alfa-2a, peginterferon alfa-2b and ribavirin</td>
<td>Unable to calculate</td>
</tr>
<tr>
<td>Ranibizumab - assumed one vial per eye</td>
<td>0.87</td>
</tr>
<tr>
<td>Ranibizumab - assumed one vial per patient, for both eyes</td>
<td>0.95</td>
</tr>
<tr>
<td>Renal cell carcinoma – sunitinib and pazopanib</td>
<td>0.68</td>
</tr>
<tr>
<td>Riluzole</td>
<td>0.66</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>2.09</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>0.97</td>
</tr>
</tbody>
</table>

These figures can be interpreted appropriately only 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.

- The variation approach analysed 36 medicines in 18 groups and presents data showing the utilisation of the medicines over time and by sub national area (see section 4). The use of the variation approach in this report, for the first time, has enabled a number of medicines previously excluded due to difficulties with estimates, to be included.

NICE TAs generally recommend use of a medicine 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 occur only 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, changes in prevalence or incidence, 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, estimation methods and other methods for analysing usage. Readers are invited to make suggestions to allow improved analysis of these medicines in future publications. Feedback is specifically requested to help inform how best to estimate uptake to allow meaningful interpretation of any variation across NHS organisations in future. Feedback is also requested on the variation approach adopted for the first time in this publication.
1 Introduction

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

This report is published following the 2009 PPRS agreement, which 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 NICE. The PPRS agreement between 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 an efficient and profitable pharmaceutical industry.

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 DH and the pharmaceutical industry are both committed to increasing access to innovative cost-effective medicines in the NHS. To this end:

- DH has committed to the annual publication of national and local level metrics for the uptake of medicines positively appraised by NICE.
- The pharmaceutical industry has committed to support this initiative through sharing of appropriate datasets on medicines usage.
- The metrics will be published through suitable channels on an on-going basis.

The 2014 PPRS agreement was implemented on 1 January 2014, and contains a commitment to continue to produce national medicine metrics in the future.

1.1 Overview of this report

This fourth report considers 54 medicines covering 47 TAs. Data on the number of patients diagnosed with specific conditions or being treated is not collected centrally by the NHS. Instead, this report uses an estimate and a variation approach to show the use of NICE recommended medicines within the NHS in England and variation between organisations.

1. In line with previous reports, an estimate approach compares estimated predicted use (calculated using the estimated number of eligible patients and the amount of medicine they would be expected to receive) with observed use where this is technically appropriate. This approach considers 18 medicines.

2. A variation approach shows variation in medicine use over time and across NHS organisations. This approach considers 36 medicines. This approach has been adopted to enable a wider range of medicines to be included in the report and specifically to include those medicines where significant uncertainty remains in establishing an estimate of the eligible patient population and/or estimate of usage. Difficulties in establishing an estimate included but were not limited to: 1) medicines with more than one licensed indication where proportional usage could not be established; or 2) where multiple treatment options exist and it is not possible to establish the proportion of patients likely to receive a particular treatment. Some medicines were deliberately selected for this approach, rather than an estimate approach, where it was agreed that this would be of more value to readers. For example the variation approach gives more
insight to the use of medicines where use is well established and uptake is known to be greater than expected.

There are three main sectors for the supply of medicines to patients. These are primary care, secondary care and where prescribing is initiated in secondary care but the medicines are supplied in the community.

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 (FP10HP), and secondary care data (Hospital Pharmacy Audit Index (HPAI)). In some cases data provided by the manufacturer was used. See section 6, sources and definitions, for more information on the data sources used in this report.

1.2 Previous reports

The first “Use of NICE Appraised Medicines” report was published in September 2009\(^3\). It considered 26 medicines positively appraised by NICE, covering 13 TAs. 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 therapy groups, relating to 29 TAs. 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. For one drug group use was lower on one set of assumptions, and higher on the alternative.

The third report was published in October 2012\(^5\), and reported on use of medicines in both 2010 and 2011. It considered 52 medicines in 25 groups, covering 35 TAs. For the 13 groups where a comparison could be made (presented in section one of the results), observed use by the NHS in England was higher than the predicted use for six and lower for six. For one drug group use was lower on one measure, and higher on another. This report included an additional section for those appraisals where a valid comparison could not be made, but there was value in outlining the methodological difficulties and the reasons why the comparison could not be made. These were presented along with a series of questions inviting readers to suggest improvements to the method or data. In addition an approach to analysing the use of biologics medicines for the treatment of rheumatoid arthritis was presented.

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1.3 Report production

This report is the result of collaborative work between HSCIC and NICE, with contributions from the pharmaceutical industry. The following groups were established to deliver this work:

- The Metrics Oversight Group (MOG) was established in September 2011 to provide strategic leadership and direction to this work. MOG is jointly chaired by the HSCIC Head of Profession for Statistics and a member of the ABPI Board of Management. The MOG membership consists of representatives from DH, the pharmaceutical industry, NICE, HSCIC and the NHS.

- The Metrics Expert Group (MEG) was established in September 2011 to be responsible for the development of the metrics. MEG is chaired by a DH Statistician, and the membership is comprised of representatives from DH, HSCIC, NICE, and the pharmaceutical industry. MEG reports to the MOG, with the chair of MEG attending MOG meetings.

- A technical sub group of MEG was established for the 2012 report. This included members with the necessary technical skills to support the technical development of metrics for medicines included in the variation approach.

- A project management group was established to help manage the production of this work.

1.3.1 Pharmaceutical industry engagement

Industry engagement is an important component in producing this report, and ensuring better understanding of the report’s findings.

Industry engagement commenced after the initial MEG process to select medicines for potential inclusion in the report. The ABPI identified contacts within ABPI member companies. In addition, non-ABPI member (but PPRS member) companies have also been included in this process.

The engagement process required different arrangements based on the medicines selected for inclusion within the report, and whether the estimate or variation approach was being used (see section 2).

Further direct dialogue was necessary between NICE, HSCIC and industry for the following specific areas:

- Hepatitis C: Roche, MSD and Janssen
- Sunitinib and Pazopanib: Pfizer and GSK
- Multiple Myeloma medicines: Celgene and Janssen
- Carmustine implants: Archimedes

A total of 21 companies engaged directly. These were: Amgen, Archimedes, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Celgene, GSK, Janssen, Lilly, Lundbeck, Menarini, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Shire, Takeda, UCB. However, not all of the medicines discussed are included within the final report due to data or methodological issues, see Appendix A.
1.4 Experimental status

This report is released as an ‘experimental’ statistic\(^6\) due to methodological and data complexities involved in producing the results. Progress has been made on a number of the issues identified in previous reports, however these issues are complex and further work is needed (see section 5). These statistics are being published as they have considerable immediate value to readers however it is important that readers understand that cautions apply to the interpretation of this data.

1.4.1 Report development

The main developments to this publication are:

- The development of the variation approach, which is an additional way of showing the use of medicines, and has enabled a greater range of medicines to be included.

- The presentation of data under the new NHS structure. The impact of the re-organisation of the NHS from 1 April 2013 (following the Health and Social Care Act 2012) has been significant. As this report includes data to 31 December 2012 (prior to the re-organisation), the data used was originally recorded under Primary Care Trusts (PCTs) and Strategic Health Authorities (SHAs). Following discussions at MEG and MOG, it was agreed that this report would have more value to readers if data is presented under the new NHS geographies, i.e. AT and CCG levels. This required the data suppliers (IMS Health and the Business Services Authority (BSA)) to reorganise and rebuild their data to assign usage from the old geographies to the new geographies. This was a substantial piece of work for both organisations, and this contribution is much appreciated. MEG agreed that due to the work involved and the complexities in doing this, that it was only appropriate to map this data back for three years (2012, 2011 and 2010).

- Development of some estimates, particularly those in section two of the previous report, or where legitimate concerns had been raised.

1.4.2 Limitations of this report

Ideally this report would give the numbers of eligible patients and report the proportion who were treated in accordance with the relevant TA. However as the NHS does not routinely record such information in a nationally available form, then this report uses other approaches to assess medicine use.

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.

- Some medicines have multiple indications of which one or more indications have not been positively appraised by NICE

- Medicine recommended as one of a number of options for treatment.

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\(^6\) Experimental statistics are a concept used for statistics that are not fully developed, are undergoing evaluation, and do not yet meet the quality standards of National/Official Statistics.
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 relevant in the London area and where more tertiary centres exist.
- Lack of data from some mental health trusts.
- Lack of data for some medicines supplied via the homecare or outsourcing routes or supplied from specialist aseptic units which are not uniformly recorded in pharmacy systems.

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. Further details are given within the report.

1.4.3 Feedback

There is an expectation that these metrics will be developed further, taking account of informed feedback from readers. Feedback from the previous report has been considered in the drafting of this report. Please use the associated feedback form, which includes questions and requests, general comments and suggestions.
2 Method

The aim of this report is to show the use of NICE positively appraised medicines in the NHS in England, during 2012. This section of the report describes the methods used to develop the metrics and collate data on usage of medicines. For this report, an estimate and a variation approach have been used.

It should be noted that irrespective of the method by which a medicine is reported, 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. Caution should also be used in interpreting the results as there are limitations in the methods and data used to produce them (see sections 1.4.2 and 6). No measure of uncertainty, such as confidence intervals, is applied.

Figure 1 shows the main steps taken to develop the metrics in this report. Details for each step are contained in the following pages.
2.1 Medicine selection

A development process for selecting the medicines for inclusion was used to allow for the introduction of the variation method. This was based on the process used in earlier reports. The starting point was to review the medicines that had been included in last year’s report, followed by consideration of the previously excluded medicines and newer appraised medicines. For previous reports, the MEG had agreed a series of inclusion and exclusion criteria which would provide an initial list of medicines to be considered for inclusion in the report. This criterion had been agreed with MOG, and medicines were therefore 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.

The medicines were considered for either the estimate or variation approach. Those medicines that had been in section one of the previous report were selected again for the estimate approach, unless there had been a material change, where stakeholders in the report raised legitimate concerns around a previously published estimate.

At the end of these discussions, a list of medicines was proposed for inclusion using either the estimate or variation approach.

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 indications and there was no data to separate out usage for appraised indications.
- There was significant off-licence usage and no data exists to separate this out.
- There are complexities around: dosages, the choice of treatment, treatment length (which can vary according to tolerance) and patient and/or clinician choice
- The estimated eligible population was thought to be very small
- The medicine was appraised after the 1 September 2011 and so a full year of use following appraisal was not available. Note this is less important for the variation approach.

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

**2.2 Method for estimate approach**

The estimate approach compares estimated predicted use (calculated using the estimated number of eligible patients, the average dose and average length of treatment) with observed use.

**2.2.1 Estimates of the eligible patient population**

For those medicines included in section one of the previous year’s report the estimated eligible population were updated using the mid-year 2011 population figures for England.

For medicines appearing as an estimate for the first time or those included in section two of the previous report, an estimated population was produced. Data was sought from a number of different sources to refine the population numbers for the particular indications and circumstances detailed in the NICE TA. The data reviewed included: epidemiological data such as the prevalence of a disease, proportions of patients at a particular stage of a disease, and their likely treatment history. For some medicines additional information was
required, for example, the proportion of patients likely to discontinue treatment or choose an alternative.

CCGs and NHS England have 3 months following publication of a TA to comply with the recommendations under section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013. This does not mean that the estimated number of patients will be treated, or volume of medicine used, immediately following publication of guidance. There 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**

Costing tools are provided by NICE to support the implementation of most TA guidance. The costing templates are an aid for financial planning purposes and enable users to estimate the local cost impact of implementing guidance at the time of publication. They are a tool to facilitate implementation and so the figures generated by their use should be viewed only as an estimate and they should not be interpreted as NICE guidance in terms of desirable or maximum/minimum figures.

The assumptions used to generate the costing templates are based on peer reviewed literature, data sources, expert opinion and other information. Users of the costing templates are encouraged to modify these assumptions to more accurately reflect their own local circumstances. For those medicines appearing as an estimate for the first time or those presented in section two of last year’s 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. A similar process was undertaken last year for those medicines appearing in section one of that report and are now presented as estimates in this year’s report.

Examples of some of the sources of information used to generate the costing template assumptions are:

- 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.

For medicines with multiple indications, only those indications appraised by NICE were identified. Eligible populations were developed on an indication by indication basis. The separate indication estimates were then combined to produce an overall estimate. Indications not appraised by NICE were excluded from the estimate of the eligible population. Where a medicine has an indicated use not appraised by NICE this could give the impression of over usage, even if this is not the case.

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Manufacturer input to NICE estimates

Manufacturer input was requested for those medicines where a material change had been made to the eligible population calculation. Updating an estimate calculation with the mid-year 2011 population was not considered to be a material change.

For new estimates or those with a material change, the draft estimates were sent to the relevant manufacturers with a request for comments and feedback on the estimate calculations and the supporting data used to parameterise them. Company feedback was then critically appraised and where appropriate, the draft estimate was updated.

For some medicines, to overcome issues identified in the previous report, additional information was sought from the pharmaceutical manufacturers. This information was critically appraised to assess its potential for incorporation. The information was required to be robust, publicly available and verifiable.

Estimate development in the absence of a costing template

NICE do not produce a costing template where the cost impact of a technology is not considered to be significant, or when estimating the cost of impact is not possible. In addition, costing templates were not produced for guidance produced prior to January 2005.

In the absence of a costing template 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 reports and publications by Royal Societies, DH and the HSCIC (among others) and online databases such as the Office for National Statistics (ONS).

2. Where appropriate, the use of primary data sources such as Hospital Episode Statistics (HES) and IMS Health’s Disease Analyser database (containing pseudonymous patient information extracted from a sample of GP practice clinical systems).

3. Consultation with clinical experts and consideration of expert opinion used in other templates / sources of evidence for the same therapeutic area.

4. Consideration of evidence from companies.

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 2012 based on 2013 data or publications.

2.2.2 Estimates of usage (volume)

Eligible patient population estimates were used to calculate the total expected volume of medicine at a national level. Where available, Defined Daily Doses (DDDs) as defined by the World Health Organisation (WHO) were used. For those medicines where DDDs were not available or were not suitable an average dosage was agreed with experts and manufacturers.

At a sub-national level total volume was allocated proportionally across organisations based on population estimates obtained from the ONS. Although not in existence during the period covered by this report, the expected volumes were allocated using the new NHS organisations created through the Health and Social Care Act 2012. Expected usage volumes have been produced for CCGs and ATs. At the time of writing this report CCG and AT populations estimates were only available for the Mid-2011 population and so this structure has been applied to all years covered by the report.
2.2.3 Observed use

Observed use of the medicines under consideration was obtained by the HSCIC through its routine access to data on prescriptions dispensed in the community (supplied by the NHS BSA) and use of medicines in hospitals (supplied by IMS Health). Usage data was converted to physical quantities and, where appropriate, to DDDs to allow comparison with the estimates. In some cases the companies advised that the data available was incomplete and so they provided their own data. See section 6 (sources and definitions) for more details on data sources.

2.2.4 Comparison of expected and observed use

Observed use is compared with the estimated use to indicate whether use is higher or lower than expected.

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 ATs and CCGs 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.

2.3 Method for variation approach

The Oxford dictionary defines an estimate as ‘an approximate calculation’. The estimates developed for the purpose of this report are in line with this definition. This is due to the many uncertainties inherent in predicting clinical usage and the pace of adoption of new technologies in different localities with varying population needs and by many different clinical teams. Depending on the available approach to devising the estimate, the necessary approximation may not meet with the more exacting role of a “benchmark” used to identify under or over implementation of a new technology.

A reasonable conclusion is that, at least in some instances, an estimate-based approach to describing uptake of NICE appraised medicines has limitations. Previous publications have included requests for suggestions for additional, novel approaches to support this work.

The variation approach is a well-established technique utilised for highlighting variation in prescribing practice across organisations and comparing changes over time. For example, It is employed in prescribing comparators used within the Quality, Innovation, Productivity and Prevention (QIPP) medicines and procurement work stream and in reporting achievement against Quality and Outcomes Framework (QOF) indicators.

This approach can support local discussion and decisions in reviewing the appropriateness of current prescribing, with the aim of reducing variation and a movement of the mean in the appropriate direction over time. Whilst some variation in practice is expected (due to
demographic differences, clinical need, and patient preferences\textsuperscript{8} wide, ‘unwarranted’ variation in practice is also seen, and this approach can be used to challenge existing patterns of care\textsuperscript{9} \textsuperscript{10} \textsuperscript{11}. In the past unwarranted variation has been attributed to failure to keep up to date with clinical evidence, misinterpretation of available evidence, unreliability of systems designed to support clinical practice, or poor communication across clinical boundaries within healthcare systems\textsuperscript{12}. However, there is now a greater recognition that the paths from research to improved health outcomes are complex\textsuperscript{13} and decision making is often compromised by cognitive biases\textsuperscript{14}. Reducing unwarranted variation while honouring valid variation makes care both more evidence-based and more personalised\textsuperscript{15}.

The variation approach does not allow any assessment of the level of compliance by organisations with NICE recommendations, nor does it provide a benchmark or target.

2.3.1 Numerator and denominator development

To represent variation it was necessary to establish a comparator (comprising of a numerator and denominator) for the selected medicines. The proposed comparators were first discussed by the technical group and then recommended to MEG where a decision was made.

Development of the comparators required an understanding of the condition being treated, knowledge of other treatment options and of the doses of the medicines. There are two main types of comparator:

1. Use of recommended medicines (numerator) as a percentage of all other possible options (denominator) referred to as ‘per cent use’ in section 4 when describing the variation approach taken.

2. Use of recommended medicines (numerator) per population (denominator) referred to as ‘use per patient’ in section 4 when describing the variation approach taken.

For some medicines it was relatively straightforward to identify a suitable comparator, however for other medicines the solution was more difficult and careful consideration was required to establish the most appropriate numerators and denominators to avoid being misleading. The complexity generally related to the following issues:

- The availability of appropriate data for measuring medicine use. For example where options for treatment are supplied predominantly in different sectors (primary care or secondary care or via the FP10 supply route) or dosing regimens are variable.
- The availability of appropriate data for measuring populations. For example where medicines are intended for use in specific age and/or gender groups or for patients with certain conditions such as diabetes, osteoporosis, or cardiovascular disease.

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\textsuperscript{8} Petrova M, Dale J, Fulford KWM. Values-based practice in primary care; easing the tensions between individual values, ethical principles and best evidence. BJGP 2006; 56: 703-9.

\textsuperscript{9} See http://www.rightcare.nhs.uk/atlas/

\textsuperscript{10} See http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_117977.pdf


\textsuperscript{13} Galziou P, Haynes B. The paths from research to improved health outcomes. Evid Based Med 2005; 10: 4-7.

\textsuperscript{14} National Prescribing Centre. Supporting the adoption of evidence into practice. MeReC Bulletin 2010; 22: 2.

Manufacturer input to NICE variation approach
For those medicines where limitations in the data prevented the development of an estimate, the variation approach was adopted following discussion at MEG.

Once selected for this approach, draft charts were sent to the relevant manufacturers. Feedback and comments were sought on the numerator and denominator chosen to represent variation for a particular medicine or group of medicines and to ask manufacturers to propose alternative statistical measures to describe variation. Company feedback was then critically appraised and where appropriate, the draft charts were updated.

2.3.2 Results
Throughout the process of developing the variation measure, the MEG group (and technical sub-group) discussed ways of showing statistical variation in a manner that would be user friendly. Two types of chart have been developed to visually represent this approach to describing variation. These are a “box and whisker” chart and an “all data points” chart.

Figure 2 Example: Box and Whisker chart

A box and whisker diagram illustrates the spread of a set of data during a specified period of time (quarters or annually). The box gives the range of the middle 50 per cent normally called the inter-quartile range. It represents the range of the data between 25 per cent (the lower quartile) and 75 per cent (the upper quartile). The line in the box represents the median, which is the middle value of the data when it is arranged in ascending order. The two whiskers (the lines) show the upper and lower quartile range. The horizontal bar at the end of the whisker shows the highest and lowest values. The light blue line across the chart shows the mean.
An all data points chart shows individual data points for each organisation during a specified period of time (quarters or annually). Data for each period are plotted in a line with each narrow horizontal bar representing a single organisation. This type of chart enables the reader to see the distribution of observations relative to other organisations during the same period of time. The light blue line across the chart shows the mean.

A discussion of the results has been provided for each medicine or group of medicines to assist readers in interpreting the results.
3 Results for estimate approach

This section shows results for the estimate approach and covers the following medicines/groups of medicines:

3.1 Alzheimer’s disease - donepezil, galantamine, rivastigmine, memantine
3.2 Carmustine implants
3.3 Diabetes (type 2) - exenatide and liraglutide
3.4 Diabetes (type 1 and type 2) - insulin glargine and insulin detemir
3.5 Hepatitis C – peginterferon alfa-2a, peginterferon alfa-2b and ribavirin
3.6 Ranibizumab
3.7 Renal cell carcinoma - sunitinib and pazopanib
3.8 Riluzole
3.9 Temozolomide
3.10 Trastuzumab

Each section is divided into:

- Summary: This contains details of the licensed indications and the relevant NICE appraisals for each technology considered. For the complete details of the TAs, please refer to the guidance documents, available on the NICE website (http://www.nice.org.uk/guidance/).
- Estimate of eligible patients: This describes the method by which the number of patients was estimated for 2012.
- Estimated usage (volume): This describes the assumed use of the drug by each eligible patient, where this is possible.
- References: This shows the references used to construct the estimates.
- Observed uptake: This describes the source of the data and notes any exclusions or special processing involved.
- Results: Results are 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 AT or CCG analyses where possible. 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 or misinterpretation. CCG level analysis is possible only if use of the drug is predominantly in primary care.

In some cases further charts are provided showing the use over the last three years (2010, 2011 and 2012) and/or showing relative use of the selected medicines compared to other medicines used to treat the same indication.

Data for medicine use in hospital is taken from the HPAI database. As further explained in section 6 (sources and definitions), 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 hospital data (HPAI) is the same as in the primary care data (ePACT) 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.
3.1 Alzheimer’s Disease - donepezil, galantamine, rivastigmine, memantine

3.1.1 Summary

Donepezil and galantamine are indicated for the symptomatic treatment of mild to moderately severe Alzheimer’s dementia; rivastigmine for mild to moderately severe Alzheimer’s dementia and the treatment of mild to moderately severe dementia in patients with idiopathic Parkinson’s disease, and memantine for the treatment of patients with moderate to severe Alzheimer’s disease (SPC).

NICE has reviewed the earlier appraisal for these drugs for the treatment of Alzheimer’s disease (NICE TA 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:

- Acetylcholinesterase (AChE) inhibitors - 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.

3.1.2 Estimate of eligible patients

<table>
<thead>
<tr>
<th>Prevalence of dementia</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females:</td>
<td>457,224</td>
</tr>
<tr>
<td>Males:</td>
<td>301,593</td>
</tr>
<tr>
<td>Subtotal:</td>
<td>758,817</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proportion of people with dementia that have</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease:</td>
<td>470,467</td>
</tr>
<tr>
<td>Proportion diagnosed:</td>
<td>202,301</td>
</tr>
</tbody>
</table>
## Mild Alzheimer's Disease

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated cases with mild Alzheimer's disease (MMSE score 21–26)</td>
<td>112,075</td>
<td>55.4%</td>
<td>5</td>
</tr>
<tr>
<td>Proportion of people diagnosed with mild Alzheimer's disease who are referred to a specialist</td>
<td>78,452</td>
<td>70%</td>
<td>5</td>
</tr>
<tr>
<td>Proportion of people diagnosed with mild Alzheimer's disease who are referred to a specialist and have some form of treatment</td>
<td>71,549</td>
<td>91.2%</td>
<td>5</td>
</tr>
<tr>
<td>Proportion of treated people with mild Alzheimer's disease taking AChE inhibitors</td>
<td>66,325</td>
<td>92.7%</td>
<td>5</td>
</tr>
<tr>
<td>Compliance with treatment</td>
<td>53,060</td>
<td>80%</td>
<td>5</td>
</tr>
<tr>
<td>Proportion treated with donepezil</td>
<td>36,452</td>
<td>68.7%</td>
<td>6</td>
</tr>
<tr>
<td>Proportion treated with galantamine</td>
<td>10,665</td>
<td>20.1%</td>
<td>6</td>
</tr>
<tr>
<td>Proportion treated with rivastigmine</td>
<td>5,943</td>
<td>11.2%</td>
<td>6</td>
</tr>
</tbody>
</table>

## Moderate Alzheimer's Disease

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of people diagnosed with Alzheimer's disease whose disease is moderate</td>
<td>64,939</td>
<td>32.1%</td>
<td>5</td>
</tr>
<tr>
<td>Proportion of people diagnosed with moderate Alzheimer's disease who are referred to a specialist</td>
<td>55,198</td>
<td>85%</td>
<td>5</td>
</tr>
<tr>
<td>Proportion of people diagnosed with moderate Alzheimer's disease referred to a specialist and having some form of treatment</td>
<td>52,990</td>
<td>96%</td>
<td>5</td>
</tr>
<tr>
<td>Proportion of treated people with moderate Alzheimer's disease taking AChE inhibitors or memantine</td>
<td>51,400</td>
<td>97%</td>
<td>5</td>
</tr>
<tr>
<td>Compliance of people with Alzheimer's that are diagnosed with moderate Alzheimer's, are referred to a specialist and are treated with AChE inhibitors or memantine</td>
<td>41,120</td>
<td>80%</td>
<td>5</td>
</tr>
<tr>
<td>Proportion treated with memantine</td>
<td>9,030</td>
<td>21.6%</td>
<td>6</td>
</tr>
<tr>
<td>Proportion treated with AChE inhibitors</td>
<td>32,238</td>
<td>78.4%</td>
<td>6</td>
</tr>
<tr>
<td>Proportion treated with donepezil</td>
<td>22,148</td>
<td>68.7%</td>
<td>6</td>
</tr>
<tr>
<td>Proportion treated with galantamine</td>
<td>6,480</td>
<td>20.1%</td>
<td>6</td>
</tr>
<tr>
<td>Proportion treated with rivastigmine</td>
<td>3,611</td>
<td>11.2%</td>
<td>6</td>
</tr>
</tbody>
</table>
### Severe Alzheimer’s

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of people diagnosed with Alzheimer’s disease whose disease is severe</td>
<td>25,288 (12.5%)</td>
<td>(5)</td>
</tr>
<tr>
<td>Proportion of people diagnosed with severe Alzheimer’s disease who are referred to a specialist</td>
<td>17,954 (71%)</td>
<td>(5)</td>
</tr>
<tr>
<td>Proportion of people diagnosed with severe Alzheimer’s disease referred to a specialist and having some form of treatment</td>
<td>13,448 (74.9%)</td>
<td>(5)</td>
</tr>
<tr>
<td>Proportion of treated people with severe Alzheimer’s disease treated with memantine</td>
<td>4,169 (31%)</td>
<td>(5)</td>
</tr>
<tr>
<td>Compliance of people with Alzheimer’s that are diagnosed with severe Alzheimer’s, are referred to a specialist and are treated with memantine</td>
<td>3,335 (80%)</td>
<td>(5)</td>
</tr>
</tbody>
</table>

### Total number of patients treated per year with:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Patients Treated per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>58,600</td>
</tr>
<tr>
<td>Galantamine</td>
<td>17,145</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>9,553</td>
</tr>
<tr>
<td>Memantine</td>
<td>12,365</td>
</tr>
</tbody>
</table>

**DDD**s

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

#### 3.1.3 Estimated usage (volume)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>(1.60 \times 10^8) mg</td>
</tr>
<tr>
<td>Galantamine</td>
<td>(1.00 \times 10^6) mg</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>(3.14 \times 10^7) mg</td>
</tr>
<tr>
<td>Memantine</td>
<td>(9.03 \times 10^7) mg</td>
</tr>
</tbody>
</table>

#### 3.1.4 References


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

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


3.1.5 Observed uptake
These drugs are used in both primary and secondary care and so data from ePACT, FP10HP and HPAI were used. Primary care accounted for 74.8 per cent of total use (measured in DDDs) in 2012.

3.1.6 Results
The table below shows expected and observed use and the ratio between them for 2012. The number of Alzheimer’s medicines used was 55 per cent higher than expected in 2012.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (DDDs)</th>
<th>Observed (DDDs)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>35,647,222</td>
<td>55,315,700</td>
<td>1.55</td>
</tr>
</tbody>
</table>

The chart below shows the ratio of the observed and expected use for 2012 at AT level. Expected use was apportioned to ATs using the ONS mid-2011 population aged 30 years and over. This chart shows that there is variation in use across ATs.

Figure 4 Ratio of observed to expected, Alzheimer’s medicines, at Area Team level, 2012
The chart below shows the number of DDDs per quarter for Alzheimer’s medicines using data from ePACT, FP10HP and HPAI. Note that during 2012 the patents for donepezil and galantamine expired.

**Figure 5  Number of DDDs per quarter, Alzheimer’s medicines, at National level (January 2010 – December 2012)**

[Diagram depicting the number of DDDs per quarter for Alzheimer’s medicines from January 2010 to December 2012, showing the trends for different medicines such as Total, Donepezil Hydrochloride, Galantamine, and Rivastigmine.]
3.2 Carmustine implants

3.2.1 Summary

Carmustine implants are indicated in newly-diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation. Carmustine implants are indicated for use as an adjunct to surgery in patients with recurrent histologically proved glioblastoma multiforme for whom surgical resection is indicated (SPC).

NICE has appraised carmustine implants for the treatment of newly diagnosed high-grade glioma (NICE TA guidance 121, 2007):

_Carmustine implants are recommended as a possible treatment for people with newly diagnosed high-grade glioma only if 90 per cent or more of their tumour has been removed (TA121)._  

_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 per cent 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 per cent of their tumour has been removed (TA121)._  

3.2.2 Estimate of eligible patients

<table>
<thead>
<tr>
<th>Total population</th>
<th>53,107,200</th>
<th>Reference (1)</th>
</tr>
</thead>
<tbody>
<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>1,891</td>
<td></td>
</tr>
<tr>
<td>Per cent of which have grade 3 glioma</td>
<td>25%</td>
<td>(3)</td>
</tr>
<tr>
<td>Per cent of which have grade 4 glioma (GBM)</td>
<td>75%</td>
<td>(3)</td>
</tr>
</tbody>
</table>
### Grade 3 glioma

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of grade 3 glioma</td>
<td>473</td>
</tr>
<tr>
<td>Per cent of patients that undergo surgery</td>
<td>84%</td>
</tr>
<tr>
<td>Number receiving surgery</td>
<td>397</td>
</tr>
<tr>
<td>Per cent undergoing surgery in whom 90 per cent has been resected</td>
<td>25%</td>
</tr>
<tr>
<td>Number eligible to receive carmustine implant</td>
<td>99</td>
</tr>
<tr>
<td>Per cent of patients choosing to receive carmustine implants</td>
<td>33%</td>
</tr>
<tr>
<td>Number of grade 3 patients to receive carmustine implants</td>
<td>33</td>
</tr>
<tr>
<td>Average number of implants per patient</td>
<td>6.5</td>
</tr>
</tbody>
</table>

### Grade 4 glioma (GBM)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of grade 4 glioma</td>
<td>1,418</td>
</tr>
<tr>
<td>Estimated per cent of grade 4 patients that would receive carmustine implants</td>
<td>15%</td>
</tr>
<tr>
<td>Estimated number of grade 4 that would receive carmustine implants</td>
<td>213</td>
</tr>
<tr>
<td>Average number of implants per patient</td>
<td>6.5</td>
</tr>
</tbody>
</table>

### Total number of implants

<table>
<thead>
<tr>
<th>Type</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 Glioma</td>
<td>215</td>
</tr>
<tr>
<td>Grade 4 Glioma</td>
<td>1,385</td>
</tr>
</tbody>
</table>

### 3.2.3 Estimated usage (volume)

1.23x10^4 mg

### 3.2.4 References


2. Annual incidence data have been taken from the NICE assessment report

3. The ratio of grade 3 and grade 4 gliomas has been 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 per cent of high
grade gliomas and anaplastic oligos (AO) represent about 5 per cent. 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 per cent 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. This study included patients with a newly diagnosed grade IV glioblastoma. The proportion of patients undergoing surgery was based on this study, in the absence of alternative information.

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

5a. Although patients that have had 90 per cent or more of their tumour resected would be eligible to receive carmustine implants, it is estimated a proportion would not receive the treatment. The figure of 33 per cent 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 suggests that a minority of the grade 4 patients would receive carmustine implants, estimated at being 15 per cent. 85 per cent would be treated with temozolomide.

8. TA 121 Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma, August 2010. Each implant contains 7.7mg of carmustine. (NICE TA121)

### 3.2.5 Observed uptake

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

### 3.2.6 Results

The table below shows expected and observed use and the ratio between them for 2012. The number of implants used was 16 per cent lower than expected in 2012.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (implants)</th>
<th>Observed (implants)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>1,600</td>
<td>1,340</td>
<td>0.84</td>
</tr>
</tbody>
</table>

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. As the number of expected patients is low a sub-national analysis would not be appropriate.
Figure 6 shows the number of carmustine implants using data from the HPAI.

Figure 6  Number of carmustine implants, at National level (2005 - 2012)
3.3 Diabetes (type 2) - exenatide and liraglutide

3.3.1 Summary

Exenatide is indicated for treatment of type 2 diabetes mellitus in combination with:

- metformin
- sulphonylureas
- thiazolidinediones
- metformin and a sulphonylurea
- metformin and a thiazolidinedione

in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

Exenatide is also indicated as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents (SPC).

Liraglutide is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with:

- metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea
- metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy (SPC).

NICE TA203 (Oct 2010) states:

*Liraglutide in triple therapy regimens (in combination with metformin and a sulfonylurea, or metformin and a thiazolidinedione) is recommended for the treatment of type 2 diabetes, only when glycaemic control is inadequate, and the patient has:

- a body mass index of 35 kg/m² or over and is of European descent (with appropriate adjustment for other ethnic groups) and weight-related psychological or medical problems, or
- a body mass index of less than 35 kg/m², and insulin would be unacceptable for occupational reasons or weight loss would benefit other significant obesity-related comorbidities.

NICE TA248 (Feb 2012) states:

*Prolonged-release exenatide in triple therapy regimens (that is in combination with metformin and a sulphphonylurea, or metformin and a thiazolidinedione) is recommended as a treatment option for people with type 2 diabetes as described in 'Type 2 diabetes: the management of type 2 diabetes (NICE Clinical Guideline (CG) 87); that is when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5 per cent [59 mmol/mol] or other higher level agreed with the individual), and the person has:
• a body mass index (BMI) ≥ 35 kg/m² in those of European family origin (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or

• a BMI < 35 kg/m², and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

NICE CG87 (May 2009) states:

Consider adding a GLP-1 mimetic (exenatide) as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5 per cent, or other higher level agreed with the individual) and the person has:

• a body mass index (BMI) ≥ 35.0 kg/m² in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or

• a BMI < 35.0 kg/m² and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

Only continue GLP-1 mimetic (exenatide) therapy if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA1c and a weight loss of at least 3 per cent of initial body weight at 6 months).

### 3.3.2 Estimate of eligible patients

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population for England</td>
<td>53,107,200</td>
<td>(1)</td>
</tr>
<tr>
<td>England population 17 years or older</td>
<td>42,433,414</td>
<td>(1)</td>
</tr>
<tr>
<td>Estimated prevalence of diabetes mellitus</td>
<td>5.80%</td>
<td>2,461,138</td>
</tr>
<tr>
<td>Estimated proportion of type 2 diabetes mellitus</td>
<td>90%</td>
<td>2,215,024</td>
</tr>
<tr>
<td>Proportion of people receiving medication</td>
<td>72%</td>
<td>1,594,817</td>
</tr>
<tr>
<td>Proportion of people treated with GLP-1 receptor agonists</td>
<td>2.80%</td>
<td>44,655</td>
</tr>
<tr>
<td>Estimated eligible population for exenatide and liraglutide:</td>
<td>44,655</td>
<td></td>
</tr>
</tbody>
</table>
3.3.3 Estimated usage (volume)
NICE guidelines do not specify which of the medicines (exenatide or liraglutide) should be used. Therefore only an overall dosage can be estimated:

- Eligible population for exenatide and liraglutide: 44,655
- Defined daily dose being: exenatide 0.286 mg or liraglutide 1.2 mg
- Total daily doses: 44,655 x 366 x 1 daily dose
- Total daily doses: \(1.63 \times 10^7\) defined daily doses

3.3.4 References
4. NICE TA guidance 248 Diabetes (type 2) - exenatide (prolonged release) costing statement
5. NICE TA guidance 203, costing template for liraglutide for the treatment of type 2 diabetes mellitus
6. NICE TA guidance 203, costing template for liraglutide for the treatment of type 2 diabetes mellitus costing template and report
7. NICE CG 87, Type 2 diabetes: newer agents.

3.3.5 Observed uptake
These drugs are used predominantly within the primary care sector, however the national estimate includes data from ePACT, FP10HP and HPAI.

3.3.6 Results
The table below shows expected and observed use and the ratio between them for 2012. The data covers primary care use and shows that use was 3 per cent 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>2012</td>
<td>16,343,730</td>
<td>15,893,102</td>
<td>0.97</td>
</tr>
</tbody>
</table>
The chart below shows the ratio of the observed and expected use for 2012 at CCG level, using only data from ePACT. The proportion of CCGs with a ratio of greater than one was 37.4 per cent in 2012.

**Figure 7  Ratio of observed to expected for exenatide and liraglutide, at CCG level, 2012**
Figure 8 shows the number of DDDs by quarter for exenatide and liraglutide. Data is taken from ePACT.

**Figure 8  Number of DDDs for exenatide and liraglutide, at National level (January 2010 - December 2012)**

![Graph showing the number of DDDs for exenatide and liraglutide](image)

Further information on the prescribing of medicines used in the management of diabetes is available in the HSCIC report: Prescribing for Diabetes, England 2005-06 to 2012-13\(^\text{16}\).

---

3.4 Diabetes (type 1 and type 2) - insulin glargine and insulin detemir

3.4.1 Summary

Insulin glargine and insulin detemir are indicated for the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above (SPC).

Insulin glargine has been appraised by NICE for the treatment of diabetes (NICE TA 53, 2002). Recommendations in this appraisal relating to type 2 diabetes have been replaced by NICE CG 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:** (NICE CG 87)
  - 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
- **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.
3.4.2 Estimate of eligible patients

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>England population (17 years or older)</td>
<td>42,433,414</td>
<td>(1)</td>
</tr>
<tr>
<td>Diabetes prevalence in England (17 years or older)</td>
<td>2,461,138 (5.8%)</td>
<td>(2)</td>
</tr>
<tr>
<td>Proportion of diabetes patients with type 1 diabetes (17 years or older)</td>
<td>246,114 (10%)</td>
<td>(3)</td>
</tr>
<tr>
<td>Proportion of diabetes patients with type 2 diabetes (17 years or older)</td>
<td>2,215,024 (90%)</td>
<td>(3)</td>
</tr>
<tr>
<td>Type 1 diabetes patients in England &lt; 17 years</td>
<td>20,488</td>
<td>(4)</td>
</tr>
<tr>
<td>Type 2 diabetes patients in England &lt; 17 years</td>
<td>328</td>
<td>(4)</td>
</tr>
<tr>
<td>Total type 1 diabetes patients (all ages)</td>
<td>266,602</td>
<td></td>
</tr>
<tr>
<td>Total type 2 diabetes patients (all ages)</td>
<td>2,215,352</td>
<td></td>
</tr>
</tbody>
</table>

**Type 1 diabetes**
Patients requiring long-acting insulin (insulin glargine or detemir)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>133,301 (50%)</td>
<td>(5)</td>
</tr>
</tbody>
</table>

**Type 2 diabetes**
Patients requiring long-acting insulin (insulin glargine or detemir)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>155,075 (7%)</td>
<td>(6)</td>
</tr>
</tbody>
</table>

3.4.3 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 366 days/year:

- for diabetes 1                                                                 | 4.88x10^7 daily doses      |
- for diabetes 2                                                                 | 5.68x10^7 daily doses      |
- **total**                                                                     | **1.06x10^8 daily doses**  |

3.4.4 References


5. NICE TA53, section 6.2, assuming all diabetes 1 patients require insulin treatment and subtracting 50 per cent 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 per cent to 4 per cent in years 0 and 3, respectively. A midpoint of 7 per cent has been assumed for the purpose of this report. Source: costing template accompanying NICE CG87.

3.4.5 Observed uptake

These drugs are used predominantly within the primary care sector, however the national estimate includes data from ePACT and HPAI.

3.4.6 Results

The table below shows expected and observed use and the ratio between them for 2012 and shows that use in 2012 was 3 per cent higher than expected.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (daily doses)</th>
<th>Observed (daily doses)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>105,545,616</td>
<td>108,847,619</td>
<td>1.03</td>
</tr>
</tbody>
</table>

The chart below shows the ratio of observed and expected use for 2012 by CCG, using data from ePACT only. Expected use was apportioned to CCGs using the ONS mid-2011 population aged 18 years and over estimates. The proportion of CCGs with a ratio of greater than one was 50.2 per cent in 2012.

Figure 9 Ratio of observed to expected, insulin glargine and detemir, at CCG level, 2012
The chart below shows the number of DDDs by quarter for insulin glargine and detemir, using data from ePACT.

**Figure 10** Number of DDDs for insulin glargine and detemir, at National level (January 2010 – December 2012)

Further information on the prescribing of medicines used in the management of diabetes is available in the HSCIC report: Prescribing for Diabetes, England 2005-06 to 2012-13\(^{17}\).

3.5 Hepatitis C – peginterferon alfa-2a, peginterferon alfa-2b and ribavirin

Despite significant work with pharmaceutical companies, the ABPI and HSCIC, NICE are unable to derive a sufficiently robust estimate for these medicines. The key issues are outlined below. Comments and suggestions to aid the development of appropriate metrics are welcome, as this is recognised to be a clinical area with particular difficulties in ensuring all eligible patients are treated.

3.5.1 Summary

Peginterferon is indicated for the treatment of chronic hepatitis C (CHC) in adult patients who are positive for serum hepatitis C virus ribonucleic acid (HCV-RNA). This includes patients with compensated cirrhosis and/or co-infected with clinically stable HIV.

Peginterferon in combination with ribavirin is indicated for the treatment of CHC in adult patients who are previously untreated including patients with clinically stable HIV co-infection and in adult patients who have failed previous treatment with interferon alpha (pegylated or nonpegylated) and ribavirin combination therapy or interferon alpha monotherapy.

Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin. (SPC)

NICE has appraised peginterferon alpha for the treatment of chronic hepatitis C (NICE TA 75, 2004). In 2006, peginterferon alfa and ribavirin were appraised for the treatment of mild chronic hepatitis C (NICE TA 106, 2006). A part review of both technology appraisals was made in 2010: Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (NICE TA guidance 200, 2010).

Combination therapy with peginterferon alfa and ribavirin is recommended within its licensed indications for the treatment of people aged 18 years and over with moderate to severe chronic hepatitis C (CHC), defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation (TA 75).

People with moderate to severe CHC are suitable for treatment if they have:

- not previously been treated with interferon alfa or peginterferon alfa, or
- been treated previously with interferon alfa (as monotherapy or in combination therapy) (see guidance) (TA 75).

Combination therapy, comprising peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin, is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C (TA106).

Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C for people who are unable to tolerate ribavirin, or for whom ribavirin is contraindicated (see guidance) (TA106).
Combination therapy with peginterferon alfa (2a or 2b) and ribavirin is recommended as a treatment option for adults with chronic hepatitis C:

- who have been treated previously with peginterferon alfa (2a or 2b) and ribavirin in combination, or with peginterferon alfa monotherapy, and whose condition either did not respond to treatment or responded initially to treatment but subsequently relapsed or
- who are co-infected with HIV (see guidance) (TA200).

### 3.5.2 Limitations

These medicines were in section two of the previous report because there were concerns about the robustness of the estimate. In order to overcome these limitations a collaborative working group was set up, with representatives from ABPI, NICE, HSCIC, and industry (Roche, MSD and Janssen), to address the complexities of this disease area. Expert opinion was sought to strengthen the estimate assumptions, this included clinical experts and a representative from Public Health England with a special interest in this topic.

Other options were considered to progress the estimate, including the use of a range of values. However, this could not be taken forward as it became apparent that historical under reporting of diagnosis had a greater impact on the estimate than previously anticipated. Further work is being undertaken by Public Health England and will inform future reports.

An estimated eligible patient population could not be calculated for several reasons:

- Limitations in calculating number of patients diagnosed with chronic Hepatitis C. From laboratory confirmed reports of hepatitis C it is known that about 105,000 individuals have been diagnosed positive between 1996 and 2012 in England<sup>3</sup>. Laboratory reports are known to have been under-reported by around 60% in the past<sup>1</sup>; the degree of under-reporting also varies by region and over time. The extent of under-reporting of diagnosis is unknown and this may have a significant impact on the estimated total of those diagnosed. Given this limitation the number of patients eligible to participate in treatment could not be calculated with sufficient certainty.

- The proportion of eligible patients that should participate or do not participate in treatment could not be established with sufficient certainty. Some patients may not follow the expected care pathways for a number of reasons including patient and clinical choice. Treatment may not occur immediately after diagnosis and a period of watchful waiting may be adopted for patients with mild symptoms. Most patients with chronic HCV are asymptomatic or have only mild non-specific symptoms. Patient pathways are likely to vary by region and so access to treatment services may also vary. This patient group may require additional support to access or comply with treatment.

- The proportion of patients for whom re-treatment is appropriate could not be established with sufficient certainty. This includes patients who failed to respond to initial treatment, who have relapsed and who become re-infected.

An expected volume of medicine could not be established with sufficient accuracy as robust treatment assumptions could not be developed due to limited data. It was not possible to establish with sufficient certainty the proportion of patients receiving treatment who: discontinue treatment due to adverse events, fail to respond to treatment at week 12, should
receive longer repeat treatment or are considered suitable for a shortened course of treatment. Some work was done in establishing the proportion of patients with the various hepatitis C genotypes, but forming typical treatment durations was not possible given the factors discussed above.

3.5.3 References

   Data for 2006 showed that routine laboratory reporting of individuals testing positive in 19 participating centres was thought to underestimate the numbers of diagnosed HCV infections by around 60 per cent (pp. 16).


   Numbers of laboratory reported cases were obtained from current and historic Hepatitis C in the UK reports.

4. TA200 costing template

5. TA 106 estimates that 58% of patients participate in treatment.


7. TA200: Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C
3.6 Ranibizumab

3.6.1 Summary

Ranibizumab is indicated in adults for the treatment of (SPC):

- neovascular (wet) age-related macular degeneration (AMD)
- visual impairment due to diabetic macular oedema (DME)
- visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM).

Ranibizumab has been appraised by NICE for the treatment of age-related macular degeneration (NICE TA 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 manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012).

- 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.

3.6.2 Estimate of eligible patients

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>England population (43-86 year olds)</td>
<td>22,948,000</td>
<td>(1,2)</td>
</tr>
<tr>
<td>Annual incidence of wet AMD</td>
<td>30,521 (0.13%)</td>
<td>(2)</td>
</tr>
</tbody>
</table>
### Two eyes affected:

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) Patients presenting with bilateral wet AMD</td>
<td>21,365</td>
<td>70%</td>
</tr>
<tr>
<td>of which, number of patients where one eye is suitable for treatment</td>
<td>19,229</td>
<td>90%</td>
</tr>
<tr>
<td>of which, number of patients where both eyes are suitable for treatment</td>
<td>2,136</td>
<td>10%</td>
</tr>
</tbody>
</table>

**Number of eyes affected:** 23,501

**Number of patients:** 21,365

### One eye affected:

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>B) Patients presenting with one eye affected:</td>
<td>9,156</td>
<td>30%</td>
</tr>
<tr>
<td>Additionally, proportion of patients presenting with wet AMD in one eye developing wet AMD in their second</td>
<td>916</td>
<td>10%</td>
</tr>
</tbody>
</table>

**Number of eyes affected:** 10,072

**Number of patients:** 9,156

**Total number of eyes affected:** 33,573

**Total number of patients:** 30,521

### Year one:

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated proportion of eyes meeting NICE criteria for treatment</td>
<td>26,858</td>
<td>80%</td>
</tr>
<tr>
<td>Estimated proportion of patients meeting NICE criteria for treatment</td>
<td>24,417</td>
<td>80%</td>
</tr>
</tbody>
</table>

### Year two:

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of year 1 eyes continuing treatment in year 2</td>
<td>22,829</td>
<td>85%</td>
</tr>
<tr>
<td>Proportion of year 1 patients continuing treatment in year 2</td>
<td>20,754</td>
<td>85%</td>
</tr>
</tbody>
</table>

**Total number of eyes, year one and two:** 49,687

**Total number of patients, year one and two:** 45,171

### 3.6.3 Estimated usage (volume)

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of eyes, year one and two:</td>
<td>49,687</td>
<td></td>
</tr>
<tr>
<td>Number of injections per year per eye</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Total number of injections</strong></td>
<td>298,122</td>
<td></td>
</tr>
<tr>
<td>Total number of patients, year one and two</td>
<td>45,171</td>
<td></td>
</tr>
<tr>
<td>Number of injections per year per patient</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Total number of injections (based on patients)</strong></td>
<td>271,028</td>
<td></td>
</tr>
</tbody>
</table>
3.6.4 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 per cent which equates, on average, to 0.133 per cent 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 per cent 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 per cent) presenting with bilateral wet AMD may be eligible for treatment in both eyes.

4. 8–12 per cent 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 per cent 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 per cent of patients remained in treatment at 12 months. Anecdotal evidence from discussions with UK clinicians suggests that about 80 per cent of patients continue treatment in year 2. For the purpose of this report a midpoint of 85 per cent 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.

3.6.5 Observed uptake
This drug is used solely within the secondary care sector and therefore data was taken from HPAI database.

3.6.6 Results
The standard dose of ranibizumab is 500 micrograms per eye but each vial contains larger volumes. Following feedback from the report covering 2009, the report covering 2010 and 2011 analysed use reporting both vials and volume in doses. Subsequent feedback for this report indicated that vials were a better measure than actual volume as the usual procedure would be to use a vial to treat a single patient and any surplus would be discarded.

This report shows expected and observed use and the ratio between them for 2012 based on two assumptions. The first that one vial is used for each injection in each eye, and the second that one vial would be used for one patient (assuming that where two eyes are affected, both eyes are treated at the same time).

If it is assumed that each vial can only be used to deliver one dose then use was 13 per cent lower than expected. If it is assumed that one vial is used to treat each patient the use is 5 per cent lower than expected.

Table 6 Expected and observed use for ranibizumab, 2012

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected</th>
<th>Observed</th>
<th>Ratio</th>
<th>Expected</th>
<th>Observed</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>298,122</td>
<td>258,267</td>
<td>0.87</td>
<td>271,028</td>
<td>258,267</td>
<td>0.95</td>
</tr>
</tbody>
</table>

The chart below shows the ratio of observed and expected use for both assumptions, for 2012 at AT level. Expected use was apportioned to ATs using the ONS mid-2011 population aged 43 years to 86 years estimates. This chart shows that there is variation in use across ATs.
Figure 11  Ratio of observed to expected for ranibizumab at Area Team level, 2012
The chart below shows the net ingredient cost for ranibizumab over time using HPAI data.

**Figure 12  Net Ingredient Cost for ranibizumab, at National level (2007 – 2012)**
3.7 Renal cell carcinoma - sunitinib and pazopanib

3.7.1 Summary

Sunitinib is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults. It is also indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib treatment due to resistance or intolerance. It can also be used for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults (SPC).

Pazopanib is indicated in adults for the first line treatment of advanced Renal Cell Carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease. It is also indicated for the treatment of adult patients with selective subtypes of advanced Soft Tissue Sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy (SPC).

Sunitinib has been appraised by NICE for the first line treatment of advanced and/or metastatic renal cell carcinoma (NICE TA guidance 169, 2009).

Sunitinib is recommended 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.

NICE has also appraised sunitinib for the treatment of GIST (NICE TA guidance 179, 2009).

NICE has appraised pazopanib as a first line treatment option for people with advanced renal cell carcinoma (NICE TA guidance 215, 2011).

As a first-line treatment option for people with advanced renal cell carcinoma:

- who have not received prior cytokine therapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and

- if the manufacturer provides pazopanib with a 12.5 per cent discount on the list price as agreed in the patient access scheme.
3.7.2 Estimate of eligible patients

Renal cell carcinoma

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of newly diagnosed kidney cancers</td>
<td>8,369</td>
<td>(1)</td>
</tr>
<tr>
<td>Total number of patients with renal cell carcinoma</td>
<td>7,532</td>
<td>(2)</td>
</tr>
<tr>
<td>a) From the total, patients with stage III (advanced) renal cell carcinoma</td>
<td>1,958</td>
<td>(3)</td>
</tr>
<tr>
<td>b) From the total, patients with stage IV (metastatic) renal cell carcinoma</td>
<td>1,280</td>
<td>(3)</td>
</tr>
<tr>
<td>c) From the total, patients with stage I and II renal cell carcinoma</td>
<td>4,293</td>
<td></td>
</tr>
<tr>
<td>d) Number of former stage I and II patients with recurrence</td>
<td>1,430</td>
<td>(4)</td>
</tr>
<tr>
<td>Total number of patients in the above groups (A+B+D)</td>
<td>4,668</td>
<td></td>
</tr>
</tbody>
</table>

Overall proportion of patients that present with an Eastern Cooperative Oncology Group performance status of 0 or 1, and are suitable for immunotherapy

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of renal cell carcinoma patients eligible for treatment with either sunitinib or pazopanib</td>
<td>3,174</td>
<td></td>
</tr>
</tbody>
</table>

3.7.3 Estimated usage (volume)

Sunitinib and pazopanib have both been appraised by NICE as first line treatment options for people with advanced renal cell carcinoma. These medicines have different dose regimes and so estimated volumes on a per patient basis are presented for each medicine.

Sunitinib: Renal cell carcinoma

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose per active treatment day (mg)</td>
<td>38.15</td>
<td>(6)</td>
</tr>
<tr>
<td>Total active treatment days for 5.5 cycles*</td>
<td>161</td>
<td>(7,8)</td>
</tr>
<tr>
<td>*One cycle equates to 28 days of active treatment and 14 days without</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total volume of sunitinib per patient (mg)</td>
<td>6,142</td>
<td></td>
</tr>
</tbody>
</table>

Pazopanib: Renal cell carcinoma

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose per day (mg)</td>
<td>688</td>
<td>(9)</td>
</tr>
<tr>
<td>The median duration of treatment (days)</td>
<td>243</td>
<td></td>
</tr>
<tr>
<td>Total volume of pazopanib per patient (mg)</td>
<td>167,184</td>
<td></td>
</tr>
</tbody>
</table>

3.7.4 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 per cent 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.


7. Based on manufacturer’s assumption. BNF’s recommended dosage is 50mg/once daily for four consecutive weeks with two weeks rest.


9. NICE TA215: Pazopanib for the first-line treatment of advanced renal cell carcinoma, August 2013. The manufacturer in their model assumes a dose intensity of 86 per cent, equivalent to 688 mg (p. 11 of 42).

### 3.7.5 Observed uptake

These drugs are used predominately within the secondary care sector. Data for pazopanib was taken from the HPAI database. Pfizer, the manufacturers of sunitinib, advised that the HPAI data is incomplete and provided data directly to the HSCIC. However this dataset excludes use of the drug in clinical trials, so may not represent all appropriate use. Sunitinib has also been appraised for the treatment of GIST (TA 179) and licensed for the treatment of unresectable or metastatic pancreatic neuroendocrine tumours, however this estimate only assesses use for renal cell carcinoma. Pfizer advised that 86 per cent of sunitinib use would be for renal cell carcinoma, and the HSCIC used this proportion in calculating the observed use.

For both pazopanib and sunitinib usage was extracted by mg and converted to patients using the average total volume per patient (see section 3.7.3). The number of patients for each drug was added together and compared to the number expected. This method was used as both pazopanib and sunitinib are treatment options and it is not possible to determine what proportion of patients would receive each drug.

### 3.7.6 Results

The table below shows expected and observed use and the ratio between them for 2012. This shows that observed use was 32 per cent lower than expected in 2012.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (patients)</th>
<th>Observed (patients)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>3,174</td>
<td>2,155</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Since the number of patients per Area Team is low a sub-national analysis is not appropriate.
Figure 13 shows the net ingredient cost using data from the HPAI. For sunitinib the data presented here includes all recorded use of sunitinib, and the manufacturer indicated that this data is an underestimate.

**Figure 13  Net Ingredient Cost for pazopanib and sunitinib (2007 – 2012)**
3.8 Riluzole

3.8.1 Summary

Riluzole is indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS) (SPC).

Riluzole has been appraised by NICE for the treatment of individuals with the amyotrophic lateral sclerosis (ALS) form of Motor Neurone Disease (MND) (NICE TA 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.*

3.8.2 Estimate of eligible patients

<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>England population</td>
<td>53,107,200</td>
</tr>
<tr>
<td>UK Prevalence (%)</td>
<td>0.005%</td>
</tr>
<tr>
<td>Expected patient population</td>
<td>2,655</td>
</tr>
</tbody>
</table>

3.8.3 Estimated usage (volume)

- Daily dose per patient: 100mg (3)
- Annual daily dose: 36,500mg

**Total Estimated volume**: $9.69 \times 10^7$ mg

- WHO DDD: 100 mg (4)
  - Total DDD: $9.69 \times 10^5$

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.
3.8.4 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 July 2013.
4. WHO DDD is obtained from WHO website: http://www.whocc.no/atc_ddd_index/?code=B01AC04

3.8.5 Observed uptake
Riluzole is used within both the primary and secondary sector, so data was taken from ePACT, FP10HP and HPAI. Secondary care use amounts to 21 per cent of the total use in 2012 (measured in DDDs).

3.8.6 Results
The table below shows expected and observed use and the ratio between them for 2012. Use was 66 per cent of the expected level in 2012.

Table 8 Expected and observed use for riluzole, 2012

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (DDDs)</th>
<th>Observed (DDDs)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>969,206</td>
<td>635,588</td>
<td>0.66</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. Data is taken from ePACT, FP10HP and HPAI.

**Figure 14  Net Ingredient Cost for riluzole, at National level (January 2009 – December 2012)**
3.9 Temozolomide

3.9.1 Summary

Temozolomide is indicated for the treatment of:

- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment.
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy. (SPC)

Temozolomide has been appraised by NICE for the treatment of recurrent malignant glioma (NICE TA 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 has also been appraised in combination with carmustine implants (NICE TA 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.

3.9.2 Estimate of eligible patients

<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>53,107,200</td>
</tr>
<tr>
<td>Mean annual incidence of high-grade glioma per 100,000</td>
<td>3.56</td>
</tr>
<tr>
<td>Estimated annual number of new cases</td>
<td>1,891</td>
</tr>
<tr>
<td>Proportion of patients with grade IV glioma</td>
<td>1,418 (75%)</td>
</tr>
<tr>
<td>Of those, the proportion who have a WHO status of 0 or 1</td>
<td>709 (50%)</td>
</tr>
<tr>
<td>Patients who would choose temozolomide (patient or clinical decision)</td>
<td>603 (85%)</td>
</tr>
<tr>
<td>Recurrent treatment with temozolomide according to TA23</td>
<td>150</td>
</tr>
<tr>
<td>Total:</td>
<td>753</td>
</tr>
</tbody>
</table>
3.9.3 Estimated usage (volume)

**Concominant therapy:**
Dosage: 75 mg/m$^2$ daily for 42 days concomitantly with radiotherapy  
Estimated dose per patient: 5,513 mg

**Monotherapy:**
Dosage: 150 mg/m$^2$ daily for 5 days, followed by 23 days without treatment, for a maximum of six cycles. The dose may be increased to 200 mg/m$^2$ daily in the second and subsequent cycles.
Estimated dose per patient: 7,875 mg

**Total volume:** 1.01x10$^7$ mg

3.9.4 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](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 been 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 per cent of high grade gliomas and anaplastic oligos (AO) represent about 5 per cent - 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 per cent 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 per cent; for the purpose of this report a figure of 50 per cent has been used.

5. A small minority of patients may choose not to accept temozolomide, estimated to be 15 per cent, with the other 85 per cent receiving the treatment.

6. Dosage information from the SPC for Temodal.

7. Average surface area has been taken at 1.75 m$^2$. Assuming six cycles of monotherapy at the lower value of 150mg/m$^2$, but no dropout.
3.9.5 Observed uptake
This drug is used almost entirely in secondary care and so HPAI data has been used.

3.9.6 Results
The table below shows expected and observed use and the ratio between them for 2012. Use in 2012 was 109 per cent more than expected.

### Table 9 Expected and observed use for temozolomide, 2012

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (mg)</th>
<th>Observed (mg)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>10,075,887</td>
<td>21,039,482</td>
<td>2.09</td>
</tr>
</tbody>
</table>

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

The chart below shows the net ingredient cost for temozolomide. Data is taken from the HPAI.

**Figure 15 Net Ingredient Cost for temozolomide (2001 – 2012)**
3.10 Trastuzumab

3.10.1 Summary

Trastuzumab is indicated for the treatment of patients with HER2 positive metastatic breast cancer (SPC):

- **as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.**

- **in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.**

- **in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.**

- **in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab.**

Trastuzumab is indicated for the treatment of patients with HER2 positive early breast cancer (SPC):

- **following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable),**

- **following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel,**

- **in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin,**

- **in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter.**

Trastuzumab in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease (SPC).

Trastuzumab has been appraised by NICE for the treatment of advanced breast cancer (NICE TA 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 CG 81 on advanced breast cancer was published in 2009 but does not supersede TA34.

Trastuzumab has also been appraised for the adjuvant treatment of early-stage HER2-positive breast cancer (NICE TA107, 2006):

*Trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), is recommended as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).*

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

NICE TA 208 (2010) states:

*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
- have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3 (IHC3 positive).

### 3.10.2 Estimate of eligible patients (Breast Cancer)

<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early stage and locally advanced breast cancer</strong></td>
<td></td>
</tr>
<tr>
<td>Incidence of breast cancer (females)</td>
<td>41,523 (1)</td>
</tr>
<tr>
<td>Women with early and locally advanced invasive breast cancer (stages I-III)</td>
<td>39,447 (95%) (2)</td>
</tr>
<tr>
<td>HER2 positive patients</td>
<td>5,523 (14%) (3)</td>
</tr>
<tr>
<td>Patients suitable for adjuvant treatment</td>
<td>5,020 (90.9%) (4)</td>
</tr>
<tr>
<td>Unsuitable for treatment due to risk of adverse reaction</td>
<td>196 (3.9%) (5)</td>
</tr>
<tr>
<td><strong>Total suitable early stage patients for treatment with trastuzumab</strong></td>
<td>4,824</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advanced breast cancer</strong></td>
<td></td>
</tr>
<tr>
<td>Mortality (surrogate for metastatic breast cancer incidence)</td>
<td>10,328 (6)</td>
</tr>
<tr>
<td>Metastatic breast cancer patients with HER2 over-expression</td>
<td>2,375 (23%) (7)</td>
</tr>
<tr>
<td>Estimated cardiovascular contraindications</td>
<td>238 (10%) (8)</td>
</tr>
<tr>
<td><strong>Total suitable advanced stage patients for treatment with trastuzumab</strong></td>
<td>2,137</td>
</tr>
</tbody>
</table>
3.10.3 Estimated usage (volume) (Breast Cancer)

**Early stage and locally advanced breast cancer:**
- Average patient weight: 70.7 kg (9)
- Loading dose: 8 mg/kg (10)
- Number of vials (loading dose, rounded up): 4
- Maintenance dose: 6 mg/kg (10)
- Number of vials (maintenance dose, rounded up): 3
- Average number of maintenance doses: 15.4 (11)

Total number of vials per course: 50.2
Average volume per course: 7,530 mg

**Estimated total volume (early stage and locally advanced BC)**: $3.63 \times 10^7$ mg

**Advanced breast cancer:**
- Average patient weight: 70.7 kg (9)
- Loading dose: 8 mg/kg (10)
- Number of vials (loading dose, rounded up): 4
- Maintenance dose (mg/kg): 6 mg/kg (10)
- Number of vials (maintenance dose, rounded up): 3
- Average number of maintenance doses: 12.2 (12)

Total number of vials per course: 40.6
Average volume per course: 6,090 mg

**Estimated total volume (advanced stage BC)**: $1.30 \times 10^7$ mg

**Total volume (early stage and locally advanced + advanced)**: $4.93 \times 10^7$ mg
### 3.10.4 Estimate of eligible patients (Gastric Cancer)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>53,107,200</td>
<td>(1)</td>
</tr>
<tr>
<td>Estimated annual cases of gastric cancer</td>
<td>12,560</td>
<td>(2)</td>
</tr>
<tr>
<td>Estimated proportion of people presenting with cancer of the gastro-oesophageal junction or stomach</td>
<td>60.00%</td>
<td>(3)</td>
</tr>
<tr>
<td>Number of people presenting with locally advanced or recurrent gastric cancer</td>
<td>7,536</td>
<td></td>
</tr>
<tr>
<td>Proportion of people presenting with metastatic disease</td>
<td>73.00%</td>
<td>(4)</td>
</tr>
<tr>
<td>Number of people presenting with metastatic disease</td>
<td>5,501</td>
<td></td>
</tr>
<tr>
<td>Estimated proportion who are HER2-positive</td>
<td>16.88%</td>
<td>(4)</td>
</tr>
<tr>
<td>Number of people who are HER2-positive</td>
<td>929</td>
<td></td>
</tr>
<tr>
<td>Proportion of people who have an immunohistochemistry score of 3 (IHC3)</td>
<td>62.56%</td>
<td>(5)</td>
</tr>
<tr>
<td>Number of people who have IHC3 positive score</td>
<td>581</td>
<td></td>
</tr>
<tr>
<td>Proportion that have not had prior treatment and who would be able to receive trastuzumab combination therapy</td>
<td>53.00%</td>
<td>(6)</td>
</tr>
<tr>
<td>Estimated number of people who may be treated with trastuzumab</td>
<td>308</td>
<td></td>
</tr>
</tbody>
</table>

### 3.10.5 Estimated usage (volume) (Gastric Cancer)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
<th>Reference</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>Number of loading doses</td>
<td>1</td>
<td>(7)</td>
</tr>
<tr>
<td>Number of maintenance doses</td>
<td>7</td>
<td>(7)</td>
</tr>
<tr>
<td>Total number of doses per patient (total loading &amp; maintenance)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Loading doses per average patient</td>
<td>496</td>
<td></td>
</tr>
<tr>
<td>Maintenance dose per average patient</td>
<td>372</td>
<td></td>
</tr>
<tr>
<td>Total maintenance dose (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><strong>Total volume (mg) per course</strong></td>
<td><strong>3,100</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total volume (gastric cancer)                                                | 9.55x10⁵mg           |
Total volume (early stage and locally advanced breast cancer and advanced stage breast cancer) | 4.93x10⁷mg           |
**Total volume**                                                             | **5.03x10⁷mg**       |
3.10.6 References (Breast Cancer)


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


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 co-morbidities, 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 per cent of patients who have received chemotherapy will go on to be initiated on trastuzumab.


8. Double helix patient record card study 2010. A survey of 100 oncologists. Data supplied by Roche Products Ltd. The study indicates that 6 per cent of women are ineligible for treatment with trastuzumab due to cardiovascular comorbidity. Clinical opinion indicates that a 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 per cent.

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.


11. 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.

12. 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.

13. 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.
### 3.10.7 References (Gastric Cancer)


7. TA208 NICE Guidance Herceptin Nov 2010


### 3.10.8 Observed uptake

This drug is used primarily in secondary care but the manufacturer (Roche) felt that the data collected by IMS Health was incomplete, because of non-recorded supplies via the homecare route and from aseptic units. Roche therefore provided their own usage data at national and Area Team level for this analysis.

### 3.10.9 Results

The table below shows expected and observed use (data from Roche) and the ratio between them for 2012.

<table>
<thead>
<tr>
<th>Year</th>
<th>Expected (mg)</th>
<th>Observed (mg)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>50,301,008</td>
<td>48,645,289</td>
<td>0.97</td>
</tr>
</tbody>
</table>
The chart below shows the ratio of the observed (data from Roche) and expected use for trastuzumab, for 2012 at AT level. The proportion of ATs with a ratio of greater than one was 51.9 per cent in 2012.

Figure 16  Ratio of observed to expected for Trastuzumab, at Area Team level, 2012
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.

**Figure 17  Net Ingredient Cost for Trastuzumab, at National level (2001 – 2012)**
4 Results for variation approach

This section of results for the variation approach includes the following medicines/groups of medicines:

4.1 Acute Coronary Syndromes - abciximab, eptifibatide, tirofiban
4.2 Acute Coronary Syndromes - ticagrelor, prasugrel, clopidogrel
4.3 Alitretinoin
4.4 Attention deficit hyperactivity disorder (ADHD) in children and adolescents - methylphenidate, atomoxetine and dexamfetamine
4.5 Breast cancer (early) - hormonal treatments: anastrozole, exemestane and letrozole
4.6 Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia
4.7 Febuxostat
4.8 Lung cancer (non-small cell, EGFR-TK mutation positive) - erlotinib (1st line)
4.9 Lung cancer (non-small cell, first line) – gefitinib
4.10 Multiple Myeloma - bortezomib, lenalidomide, thalidomide
4.11 Myocardial infarction (persistent ST-segment elevation) – bivalirudin
4.12 Prevention of osteoporotic fractures - denosumab
4.13 Prevention of osteoporotic fragility fractures - alendronate, etidronate, risedronate, raloxifene, strontium ranelate, and teriparatide
4.14 Prevention of stroke and systemic embolism in atrial fibrillation – dabigatran etexilate and rivaroxaban
4.15 Prevention of venous thromboembolism after hip or knee replacement surgery - dabigatran etexilate, apixaban and rivaroxaban
4.16 Prucalopride
4.17 Short-term management of insomnia - zaleplon, zolpidem and zopiclone
4.18 Smoking cessation - varenicline

Each section is divided into:

- **Summary**: This contains details of the licensed indications and the relevant NICE appraisals for each technology considered. For the complete details of the TAs, please refer to the guidance documents, available on the NICE website (http://www.nice.org.uk/guidance/).
- **Variation Approach**: This describes why and how the variation approach has been used for these medicines.
- **Results**: are presented primarily in the form of charts which show variation over time statistically using box and whisker charts and ‘all data points chart’ with each CCG or AT shown as a point. Although, two charts are used to present the variation data, the MEG felt this was required to meet the needs of different readers of the report and ensure that the presentation of variation is as clear as possible. A table is provided
showing a summary of the measures used to create the charts. Contextual information is also provided, where appropriate, to aid interpretation.

The data presented in the box and whisker and all data points charts (at AT or CCG level) is available in the accompanying Excel spreadsheet, available at: http://www.hscic.gov.uk/pubs/niceappmed12. This spreadsheet also calculates a number of statistical measures including the mean medicine usage and the coefficient of variation.

Commentary is provided on each of the medicine groups where required with reference made to points of interest and statistical data.

- References: This shows the references used.
4.1 Acute Coronary Syndromes – abciximab, eptifibatide and tirofiban

4.1.1 Summary

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

Abciximab is indicated in adults as an adjunct to heparin and acetylsalicylic acid for:

- The prevention of ischaemic cardiac complications in patients undergoing percutaneous coronary intervention (balloon angioplasty, atherectomy, and stent).
- The short-term (1-month) reduction of the risk of myocardial infarction, in patients with unstable angina, not responding to full conventional therapy who have been scheduled for percutaneous coronary intervention. (SPC)

Eptifibatide is intended for use with acetylsalicylic acid and unfractionated heparin. It is indicated for the prevention of early myocardial infarction in adults presenting with unstable angina or non-Q-wave myocardial infarction with the last episode of chest pain occurring within 24 hours and with electrocardiogram (ECG) changes and/or elevated cardiac enzymes. (SPC).

Tirofiban is indicated for the prevention of early myocardial infarction in patients presenting with unstable angina or non-Q-wave myocardial infarction with the last episode of chest pain occurring within 12 hours and with ECG changes and/or elevated cardiac enzymes. (SPC)

These medicines have been appraised by NICE for the treatment of acute coronary syndromes (NICE TA guidance 47, 2002)\(^1\). Some of the recommendations made in the appraisal were updated as part of NICE CG 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)\(^2\).

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

4.1.2 Variation approach

Abciximab, eptifibatide and tirofiban were included in section one of the “Use of NICE appraised medicines in the NHS in England – 2010 and 2011”\(^\). However, there were uncertainties regarding volumes of individual drugs as the glycoprotein inhibitors are referred to as a group within the NICE guidelines. Estimates were therefore presented assuming
minimum and maximum doses to give a lower and upper patient limit. This problem remains and these medicines are presented using the variation approach in this report.

For the variation approach a ‘use per patient’ approach is adopted. The comparator shows DDDs of abciximab, eptifibatide and tirofiban per 100,000 population\(^3\). All three drugs, appraised in separate TAs, were combined as they are all injectable medicines used short term and in secondary care. A ‘per cent use’ variation approach is not a suitable option.

DDD was chosen as the numerator as this allows the three drugs to be combined and allows for a ‘like with like’ comparison. ‘Items’ are not available for secondary care data. Cost is different for the three drugs and therefore would provide an unequal comparison.

Per 100,000 patients was chosen as the denominator. A STAR-PU weighting is not available for this group of medicines. It is not possible to define an age range in which these drugs are used.

4.1.3 Results

Figure 18 uses HPAI data to show defined daily doses of abciximab, eptifibatide and tirofiban per 100,000 population.

**Figure 18** Defined daily doses of abciximab, eptifibatide and tirofiban per 100,000 population\(^3\). Secondary care prescribing trend, by Area Team (January 2010 - December 2012)

a) Box and Whisker chart
Use of NICE appraised medicines in the NHS in England – 2012, experimental statistics

b) All data points chart

![Graph showing data points]

| NICE TA and Date | TA47: Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes (Sept - 02)  
CG94: Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction (Mar - 10) |
| Comparator (numerator/denominator) | Defined Daily Doses per 100,000 population |
| Level of Analysis | Area Team |
| Data type | Secondary care, HPAI |

The charts illustrate a reduction in the mean use of these medicines over time and a reduction in variation. This may reflect the use of alternative management options.

4.1.4 References

4.2 Acute Coronary Syndromes – ticagrelor, prasugrel and clopidogrel

4.2.1 Summary

Ticagrelor, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with Acute Coronary Syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG). (SPC)

Prasugrel, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with acute coronary syndrome (i.e., unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI). (SPC)

Clopidogrel is indicated in adults for the prevention of atherothrombotic events in:

- Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.

- Patients suffering from acute coronary syndrome:
  - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).
  - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy. (SPC)

NICE has appraised ticagrelor for the treatment of acute coronary syndromes (NICE TA guidance 236, 2011):  

*Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with acute coronary syndromes (ACS) that is, people:

- with ST-segment-elevation myocardial infarction (STEMI) – defined as ST elevation or new left bundle branch block on electrocardiogram – that cardiologists intend to treat with primary percutaneous coronary intervention (PCI) or

- with non-ST-segment-elevation myocardial infarction (NSTEMI) or

- admitted to hospital with unstable angina – defined as ST or T wave changes on electrocardiogram suggestive of ischaemia plus one of the characteristics defined in section 1.2. Before ticagrelor is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist.*
NICE has appraised prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention (NICE TA guidance 182, 2009):

**Prasugrel in combination with aspirin is recommended as an option for preventing atherothrombotic events in people with acute coronary syndromes having percutaneous coronary intervention, only when:**

- immediate primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction is necessary, or
- stent thrombosis has occurred during clopidogrel treatment, or
- the patient has diabetes mellitus.

NICE has appraised clopidogrel for use in the management of non-ST-segment-elevation acute coronary syndrome (ACS) in people who are at moderate to high risk of myocardial infarction (MI) or death (NICE TA 80, 2004). Some of the recommendations made in the appraisal were updated as part of NICE CG 94 on unstable angina and NSTEMI. TA 80 states:

*It is recommended that treatment with clopidogrel in combination with low-dose aspirin should be continued for 12 months after the most recent acute episode of non-ST-segment-elevation ACS. Thereafter, standard care, including treatment with low-dose aspirin alone, is recommended (TA80).*

### 4.2.2 Variation approach

Although grouped together under the heading of “Acute Coronary Syndromes” these medicines are used to treat different conditions within this spectrum so it was not possible to derive an estimate of the number of eligible patients. The variation approach is not limited by this issue and provides insight to changes over time and comparison between organisations.

A ‘use per patient’ variation approach is used. The comparator shows DDDs of ticagrelor, prasugrel and clopidogrel per head of population. All three drugs appraised in separate TAs, are included as they are all oral medicines used long term, predominantly in primary care but also used and/or initiated in secondary care. Whilst they are not the only medicines that are used for these indications and fulfil the above criteria, a ‘per cent use’ variation approach was considered not to be the suitable option as the therapeutics is complex and the drugs have more than indicated use.

DDD was chosen as the numerator as this allows the three drugs to be combined and allows for a ‘like with like’ comparison. 'Items' are not available for secondary care data. Cost is different for the three drugs therefore would provide an unequal comparison.

Per patient (population) was chosen as the denominator. A STAR-PU weighting is not available for this group of medicines. It is not possible to define an age range in which these drugs are used.
4.2.3 Results

Figure 19 shows DDDs of ticagrelor, prasugrel and clopidogrel combined per head of population, while Figure 20 shows the same data for ticagrelor and prasugrel alone to provide more insight into the use of these medicines. Clopidogrel is excluded from Figure 20 as the drug has a number of indications for use. All these charts use data from ePACT and HPAI.

Figure 19 Defined daily doses (DDDs) of ticagrelor, prasugrel and clopidogrel per head of population\(^5\). Primary and secondary prescribing trend, by Area Team (January 2010 - December 2012)

a) Box and Whisker chart
b) All data points chart
Figure 20  Defined daily doses (DDDs) of ticagrelor and prasugrel per head of population\textsuperscript{5}. Primary and secondary prescribing trend, by Area Team (January 2010 - December 2012)

a) Box and Whisker chart

b) All data points chart
Table 12  Variables Summary

| NICE TA and Date | TA236: Ticagrelor for the treatment of acute coronary syndromes (Oct-11).  
| TA80: Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome (Jul-04).  
| CG94: Unstable angina and NSTEMI: The early management of unstable angina and non-ST-segmented-elevation myocardial infarction (Mar-10). |

| Comparator (numerator/denominator) | Defined daily doses per head of population |
| Level of Analysis | Area Team |
| Data type | Primary (ePACT) and secondary care (HPAI) |

Figure 19a and b illustrate a stable position over 2010, with the mean increasing from January-March 2011. Uptake is increasing for all area teams from 2011 onwards.

Figure 20a and b show an increase in the mean over time and with all area teams increasing usage.

4.2.4 References

1. TA236: Ticagrelor for the treatment of acute coronary syndromes, October 2011.
4.3 Alitretinoin

4.3.1 Summary

Alitretinoin is indicated for use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids.

Patients in whom the eczema has predominantly hyperkeratotic features are more likely to respond to treatment than in those in whom the eczema predominantly presents as pompholyx. (SPC)

Alitretinoin has been appraised by NICE for the treatment of adults with severe and chronic hand eczema (NICE TA guidance 177, 2009)\textsuperscript{1}

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.

Only dermatologists, or physicians with experience in both managing severe chronic hand eczema and the use of systemic retinoids, should start and monitor treatment with alitretinoin.

The recommended dosage is 30 mg once daily for 12–24 weeks. The dosage can be reduced to 10 mg once daily if there are unacceptable adverse effects. The most frequent adverse effects seen with alitretinoin include headache, dry mouth, anaemia, flushing and erythema. Increases in cholesterol and triglyceride levels (hyperlipidaemia) have also been observed. Adverse effects are generally dose related and reversible. Alitretinoin is teratogenic and therefore contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme (as outlined in the SPC) are met. Alitretinoin should not be prescribed if the person’s eczema can be adequately controlled by standard measures, including skin protection, avoiding allergens and irritants, and treatment with potent topical corticosteroids.

4.3.2 Variation approach

Alitretinoin was included in section two of the “Use of NICE appraised medicines in the NHS in England – 2010 and 2011” report. This was because it was not possible to ascertain what proportion of patients would receive alitretinoin as opposed to other therapy options. The variation approach is not limited by this issue and provides insight to changes over time and comparison between organisations.

A ‘use per patient’ variation approach is used. The use of alitretinoin is an option and the alternatives are numerous, complex and involve topical preparations that are difficult to measure in terms of use. Also use of alitretinoin is relatively low in comparison and a ‘per cent use’ approach would not adequately highlight the uptake of the drug or variation in prescribing.
Daily defined doses was chosen as the numerator as it provides a more accurate measure of use than items and ‘items’ are not available for secondary care data. Use of ‘cost’ is an option particularly as the price is the same for both the 10mg and 30mg capsule strengths. Per patient (population) was chosen as the denominator. A STAR-PU weighting is not available for this medicine. It is not possible to define an age range in which alitretinoin is used.

### 4.3.3 Results

Figure 21 uses data from FP10HP and HPAI to show DDDs of alitretinoin per 10,000 population.

Figure 21  Defined daily doses of alitretinoin per 10,000 population\(^2\). FP10HP and HPAI prescribing trend, by Area Team (January 2010 - December 2012)

a) Box and Whisker chart
b) All data points chart

![Chart showing data points]

<table>
<thead>
<tr>
<th>Table 13  Variables Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE TA and Date</td>
</tr>
<tr>
<td>Comparator</td>
</tr>
<tr>
<td>(numerator/denominator)</td>
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<tr>
<td>Level of Analysis</td>
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<tr>
<td>Data type</td>
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The charts illustrate an increase in the mean and a reduction in the variation over the time period.

4.3.4 References

4.4 Attention deficit hyperactivity disorder (ADHD) in children and adolescents - methylphenidate, atomoxetine and dexamfetamine

4.4.1 Summary
Methylphenidate is indicated as part of a comprehensive treatment programme for attention-deficit / hyperactivity disorder (ADHD) in children aged 6 years of age and over when remedial measures alone prove insufficient. Treatment must be under the supervision of a specialist in childhood behaviour disorders. (SPC)

Atomoxetine is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children of 6 years and older, in adolescents and in adults as part of a comprehensive treatment programme. Treatment must be initiated by a specialist in the treatment of ADHD, such as a paediatrician, child/adolescent psychiatrist, or psychiatrist. Diagnosis should be made according to current DSM criteria or the guidelines in ICD. (SPC)

Dexamfetamine is indicated for narcolepsy; refractory attention deficit hyperactivity disorder (under specialist supervision) (BNF 66)

Methylphenidate, atomoxetine and dexamfetamine have been appraised by NICE for the treatment of children and adolescents with ADHD (NICE TA 98, 2006)¹:

Where drug treatment is considered appropriate, methylphenidate, atomoxetine and dexamfetamine are recommended, within their licensed indications, as options for the management of ADHD in children and adolescents.

The decision regarding which product to use should be based on the following:

- the presence of comorbid conditions (for example, tic disorders, Tourette’s syndrome, epilepsy)
- the different adverse effects of the drugs
- specific issues regarding compliance identified for the individual child or adolescent, for example problems created by the need to administer a mid-day treatment dose at school
- the potential for drug diversion (where the medication is forwarded on to others for non-prescription uses) and/or misuse
- the preferences of the child/adolescent and/or his or her parent or guardian.

If there is a choice of more than one appropriate drug, the product with the lowest cost (taking into account the cost per dose and number of daily doses) should be prescribed.

Drug treatment should only be initiated by an appropriately qualified healthcare professional with expertise in ADHD and should be based on a comprehensive assessment and diagnosis. Continued prescribing and monitoring of drug therapy may be performed by general practitioners, under shared care arrangements.
4.4.2 Variation approach

These medicines were not included in the “Use of NICE appraised medicines in the NHS in England – 2010 and 2011” report. This was because there remained considerable uncertainty on the number of adult patients who continue treatment from childhood or adolescence. Currently none of the medicines are licensed for initiation in adulthood. In addition, prescribing data does not permit analysis of usage by age group or for unlicensed use. These issues remain.

A ‘use per patient’ variation approach was used including all three drugs appraised in the TA. Since they are the only medicines that are used for this indication, a ‘per cent use’ variation approach is not a suitable option. Secondary care data is not included as use is minimal across all ATs.

‘Items’ was chosen as the numerator. Using ADQs or DDDs may influence the variation observed with prescribing of higher doses resulting in a higher comparator value and perceived greater uptake of the medicines.

Population aged under 18 years was chosen as the denominator. Whilst it is recognised that the drugs are sometimes prescribed for adults it is not possible to determine a maximum age and it is likely that the majority of prescribing is for under 18 years old. It was considered that adopting an age range of 0 to 17 years would provide a more robust weighting than total population. A STAR-PU weighting is not available for this medicine.

4.4.3 Results

Figure 22  Methylphenidate, atomoxetine and dexamfetamine items per 1,000 population aged under 18 years\(^2\). ePACT and FP10HP prescribing trend by Area Team (January 2010 - December 2012)

a) Box and Whisker chart
b) All data points chart

Table 14  Variables Summary

<table>
<thead>
<tr>
<th>NICE TA and Date:</th>
<th>TA98: Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents (Mar-06).</th>
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<tr>
<td>Comparator:</td>
<td>Items per 1,000 population aged under 18 years</td>
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<td>Level of Analysis:</td>
<td>Area Team</td>
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<tr>
<td>Data type</td>
<td>ePACT (Primary care), and FP10HP (prescriptions issued in secondary care but dispensed in the community)</td>
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Figure 23 uses ePACT and FP10HP data to show number of items prescribed for ADHD and illustrates an increase in the use of these medicines over time. Methylphenidate is the most frequently prescribed ADHD drug.

**Figure 23  Number of items for ADHD drugs (January 2010 - December 2012)**

4.4.4 References


4.5 Breast cancer (early) - hormonal treatments: anastrozole, exemestane and letrozole

4.5.1 Summary

Anastrozole is indicated for the treatment of advanced breast cancer in postmenopausal women. Efficacy has not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen. (SPC)

Exemestane is indicated for the adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2 – 3 years of initial adjuvant tamoxifen therapy.

Exemestane is also indicated for the treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy. Efficacy has not been demonstrated in patients with oestrogen receptor negative status. (SPC)

Letrozole is indicated for:

- **Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.**
- **Extended adjuvant treatment of hormone-dependent invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years.**
- **First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.**
- **Advanced breast cancer after relapse or disease progression, in women with natural or artificially induced postmenopausal endocrine status, who have previously been treated with anti-oestrogens.**
- **Neo-adjuvant treatment of postmenopausal women with hormone receptor positive, HER-2 negative breast cancer where chemotherapy is not suitable and immediate surgery not indicated.**
- **Efficacy has not been demonstrated in patients with hormone receptor negative breast cancer. (SPC)**

NICE has appraised the use of the aromatase inhibitors anastrozole, exemestane and letrozole, within the marketing authorisations for each drug at the time of this appraisal, for the treatment of early oestrogen-receptor-positive breast cancer; that is:

- **anastrozole for primary adjuvant therapy**
- **exemestane for adjuvant therapy following 2–3 years of adjuvant tamoxifen therapy**
- **letrozole for primary adjuvant therapy and extended adjuvant therapy following standard tamoxifen therapy. (NICE TA 112, 2006)**

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.
4.5.2 Variation approach

Anastrozole, exemestane and letrozole were included in section two of the “Use of NICE appraised medicines, 2010 and 2011” report. NICE has appraised these medicines for the treatment of early breast cancer. However, they also have licensed indications for the treatment of advanced breast cancer. Usage data is not available by diagnosis and so a comparison cannot be made between estimated and observed use. The variation approach is not constrained by these issues. These drugs are used predominantly in primary care.

A per cent approach was used looking at anastrozole, exemestane and letrozole items as a proportion of all breast cancer drugs in BNF 8.3.4.1. Anastrozole, exemestane and letrozole are not the only treatment options. Hormone antagonists indicated for treatment of breast cancer in BNF 8.3.4.1. in addition to anastrozole, exemestane and letrozole are Fluvastrant, Tamoxifen, and Toremifene.

Items was chosen for both the numerator and denominator as ADQs or DDDs at AT level adds no additional value and prescribing of higher doses of may influence the variation observed. Cost is different for all drugs in 8.3.4.1 and therefore would provide an unequal comparison.

4.5.3 Results

Figure 24 Anastrozole, exemestane and letrozole items as a proportion of all breast cancer drugs in BNF 8.3.4.1. Primary care prescribing trend by Area Team (January 2010 - December 2012)

a) Box and Whisker chart
b) All data points chart

![Graph showing data points]

Table 15  Variables Summary

| NICE TA and Date                                 | TA112: Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer (Nov-06). |
| Comparator (numerator/denominator)              | Anastrozole, exemestane and letrozole as a proportion of all breast cancer drugs in BNF 8.3.4.1 |
| Level of Analysis                               | Area Team |
| Source of Prescribing                           | Primary care, ePACT |

The charts show a stable position for these drugs relative to alternative treatments with a small increase in the mean overtime. The short term shift increase in the mean for October-December 2010 was due to a change in relative availability of specific medicines in BNF 8.3.4.1 in this quarter only.

4.5.4 References

4.6 Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia

4.6.1 Summary

Ezetimibe is indicated for the treatment of:

Primary Hypercholesterolaemia:

- co-administered with an HMG-CoA reductase inhibitor (statin) is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone.
- monotherapy is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated.

Homozygous Familial Hypercholesterolaemia (HoFH):

- co-administered with a statin, is indicated as adjunctive therapy to diet for use in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

Homozygous Sitosterolaemia (phytosterolaemia):

- As an adjunctive therapy to diet for use in patients with homozygous familial sitosterolaemia.
- A beneficial effect of Ezetimibe on cardiovascular morbidity and mortality has not yet been demonstrated. (SPC)

Ezetimibe has been appraised by NICE for the treatment of adults with primary (heterozygous-familial and non-familial) hypercholesterolaemia (NICE TA 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 of TA 132).

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 of TA 132)
  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 co-administered 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 read in conjunction with NICE guidance in the initiation of statin therapy (NICE TA guidance 94) and in the context of the following CGs published by NICE:

- Type 2 Diabetes – newer agents (CG87)
- Secondary prevention in primary and secondary care for patients following 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)

4.6.2 Variation approach

Ezetimibe was included in section two of the “Use of NICE appraised medicines in the NHS in England – 2010 and 2011” report as there were significant uncertainties involved in establishing an estimate of the eligible patient population. Proportional usage of individual lipid lowering therapies could not be established.

The variation approach adopts a ‘per cent use’ approach. Ezetimibe is one of a number of treatment options, and this approach allows for the use of ezetimibe to be compared against these. The eligible population for lipid modifying drugs is unknown and therefore a ‘use per patient’ approach would be influenced by prevalence.

The comparator shows number of items for ezetimibe and ezetimibe/simvastatin combinations as a percentage of the total number of prescription items for all statins, plus the total number of prescription items for combination of simvastatin/ezetimibe, plus total number of prescription items for ezetimibe alone.

Items has been adopted rather than DDDs for both the numerator and denominator as prescribing of higher doses of drugs may influence the variation observed.
4.6.3 Results

Figure 25 uses data from ePACT to show the use of ezetimibe as a proportion of other options.

**Figure 25**  Ezetimibe as a proportion of the total number of prescription items for all statins plus the items for combination of simvastatin/ezetimibe, plus items for ezetimibe alone. Primary care prescribing trend, by Clinical Commissioning Group (January 2010 – December 2012)

a) Box and Whisker chart

b) All data points chart
Table 16  Variables Summary

| Comparator (numerator/denominator) | Ezetimibe (including combinations with simvastatin) as a proportion of the total number of prescription items for all statins plus the items for combination of simvastatin/ezetimibe, plus items for ezetimibe alone. |
| Level of Analysis | Clinical Commissioning Group |
| Data type | Primary care, ePACT |

Figure 26 shows the prescribing of ezetimibe (including ezetimibe/simvastatin combinations) expressed in DDDs, in England over the time period January 2010 to December 2012, using ePACT data.

Figure 26  Primary care DDD usage of ezetimibe (including ezetimibe/simvastatin combinations) at England level (January 2010 – December 2012)
Primary care prescribing of ezetimibe increased until September 2010, and has declined since then. There remains variation between localities in the use of ezetimibe.

Ezetimibe is included as a one of the key therapeutic topics in the QIPP\(^7\) medicines use and procurement work stream.

At CCG level the mean usage of ezetimibe as a proportion of lipid lowering agents has fallen over the three year period. This reflects both a decrease in ezetimibe prescribing and an overall increase in the prescribing of items for all statins. Variation has slightly decreased, partly as localities with higher usage move closer to the mean.

### 4.6.4 References

4.7 Febuxostat

4.7.1 Summary

In adults, febuxostat is indicated for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis). (SPC)

NICE has appraised febuxostat for the management of hyperuricaemia in people with gout (NICE TA guidance 164, 2011)\(^1\).

*Febuxostat, within its marketing authorisation, is recommended as an option for the management of chronic hyperuricaemia in gout only for people who are intolerant of allopurinol (as defined in section 1.2) or for whom allopurinol is contraindicated.*

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

4.7.2 Variation approach

Febuxostat was included in section one of the “Use of NICE appraised medicines in the NHS in England – 2010 and 2011”. Febuxostat is one of a number of valid treatment options for this patient population. The NICE costing template assumes that 94 per cent of patients contraindicated to or intolerant of allopurinol would receive febuxostat. A proportion of those patients offered treatment will decline therapy and this quantity is unknown at present. This limitation could not be overcome and it was not possible to estimate the likely volume of medicine to be consumed with sufficient certainty. Further exploration is required to understand the proportion of patients allocated to febuxostat or alternative treatment. The variation approach is not limited by these issues and enables consideration of changes over time and comparison between organisations.

The variation approach adopts a ‘use per patient’ approach. Whilst febuxostat is a treatment option to allopurinol (as per NICE guidance) current use is low. Therefore a ‘per cent use’ approach would not adequately highlight the uptake of the drug or variation in prescribing.

The comparator shows tablets of febuxostat per 10,000 population aged 25 years and over\(^2,3\). The total number of tablets for febuxostat has been adopted as the numerator. This provides a more accurate measure of uptake of the drug given that the dose is either 80mg or 120mg daily and the drug is available as 80mg and 120mg tablets. DDDs or ADQs would be influenced by the dose prescribed, driven by patient requirements and response to treatment, which would influence the variation seen. Tablets provides a more accurate value for quantity than items.

Population aged 25 years and over has been adopted as the denominator. Whilst an exact age range for use of the drug cannot be determined it is reasonable to assume that patients aged 25 years and over are likely to be prescribed the drug. Excluding patients under 25 years attempts to weight the comparator for eligible population.
4.7.3 Results

Figure 27 Tablets of febuxostat per 10,000 population aged 25 years and over\(^{(2,3)}\). Primary care prescribing trend, by Area Team (April 2010 – December 2012)

a) Box and Whisker chart

b) All data points chart
Use of NICE appraised medicines in the NHS in England – 2012, experimental statistics

Table 17 Variables Summary

<table>
<thead>
<tr>
<th>NICE TA and Date</th>
<th>TA164: Febuxostat for the management of hyperuricaemia in people with gout (December-08).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>Tablets per 10,000 population aged 25 years and over</td>
</tr>
<tr>
<td>Level of Analysis</td>
<td>Area Team</td>
</tr>
<tr>
<td>Source of Prescribing</td>
<td>Primary care, ePACT</td>
</tr>
</tbody>
</table>

Data for this medicine was available from April 2010 onwards. Prescribing of this medicine has increased over time. Throughout the period covered the data has become more dispersed around the mean.

4.7.4 References

4.8 Lung cancer (non-small cell, EGFR-TK mutation positive) - erlotinib (1st line)

4.8.1 Summary

Non-Small Cell Lung Cancer (NSCLC):

- Erlotinib is indicated for the first-line treatment of patients with locally advanced or metastatic NSCLC with Epidermal Growth Factor Receptor (EGFR) activating mutations.

- Erlotinib is also indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after 4 cycles of standard platinum-based first-line chemotherapy.

- Erlotinib is also indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

- When prescribing Erlotinib, factors associated with prolonged survival should be taken into account.

- No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR-IHC negative tumours. (SPC)

Erlotinib has been appraised by NICE for the second-line treatment of NSCLC (NICE TA guidance 162, 2008) and for the first-line treatment of locally advanced or metastatic EGFR-TK mutation positive NSCLC (NICE TA guidance 258, 2012).

TA 162: 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.

TA 258: Erlotinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic NSCLC if:

- they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation and

- the manufacturer provides erlotinib at the discounted price agreed under the patient access scheme (as revised in 2012).

4.8.2 Variation approach

Erlotinib was included in section two of “Use of NICE appraised medicines in the NHS in England – 2010 and 2011” report. Erlotinib is one of a number of valid treatment options for this patient population and it was not possible to establish the proportion of patients that would receive this medicine. This limitation could not be overcome and so an estimate of the number of eligible patients could not be developed with sufficient certainty. The variation approach is not limited by these issues and shows changes over time and comparison between organisations.
The variation approach adopts a ‘use per patient’ approach which shows erlotinib (mg) per 1,000 population\(^{(3)}\). Whilst erlotinib is one treatment option, selection of the other treatment options is complex and they are also used for other indications.

Total milligrams of erlotinib has been used as the numerator. Data on items is unavailable for secondary prescribing and a DDD is unavailable.

Per 1,000 population was chosen as the denominator. A STAR-PU weighting is not available for this medicine. It is not possible to define an age range in which erlotinib is used.

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

### 4.8.3 Results

**Figure 28** Erlotinib (mg) per 1,000 population\(^{(3)}\). Secondary care prescribing trend, by Area Team (January 2010 - December 2012)

- **a) Box and Whisker chart**
b) All data points chart

Table 18  Variables Summary

<table>
<thead>
<tr>
<th>NICE TA and Date</th>
<th>TA162: Erlotinib for the treatment of non-small cell lung cancer (Nov-08 last modified Dec-12).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TA258: Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small cell lung cancer (Jun-12)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Erlotinib (mg) per 1,000 population</td>
</tr>
<tr>
<td>Level of Analysis</td>
<td>Area Team</td>
</tr>
<tr>
<td>Data type</td>
<td>Secondary care, Roche data</td>
</tr>
</tbody>
</table>

Mean volumes of erlotinib were stable although a small decrease was seen across the three year period.
4.8.4 References


4.9 Lung cancer (non-small cell, first line) – gefitinib

4.9.1 Summary

Gefitinib is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK. (SPC)

NICE has appraised gefitinib for the treatment of locally advanced or metastatic NSCLC (NICE TA guidance 192, 2010)¹

**Gefitinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic 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.

4.9.2 Variation approach

Gefitinib was included in section two of the “Use of NICE appraised medicines in the NHS in England – 2010 and 2011” report. Gefitinib is an option for treatment in patients with EGFR positive mutation status non-small cell lung cancer. Alternative therapy regimes exist and it is not known how the eligible patient population will be distributed across these options. The estimate of the proportion of patients being treated with gefitinib could not be developed due to the alternative therapies. The variation approach is not limited by these issues and enables comparison of changes over time and between organisations.

A ‘use per patient’ approach has been adopted showing gefitinib (mg) per 1,000 population². Whilst gefitinib is one treatment option, selection of the other treatment options is complex and they are also used for other indications. DDDs are not available for gefitinib or some of the alternative options and a comparison of use based on strength (mg) would provide an unfair comparison.

Total milligrams of gefitinib has been used as the numerator. Data on items is unavailable for secondary prescribing and a DDD is unavailable.

Per 1,000 population was chosen as the denominator. A STAR-PU weighting is not available for this medicine. It is not possible to define an age range in which gefitinib is used.

AstraZeneca, who manufacture this medicine, advised that the HPAI data was incomplete and provided their own figures on the number of milligrams used.
4.9.3 Results

Figure 29 Gefitinib (mg) per 1,000 population (2). Secondary care prescribing trend, by Area Team (January 2010 - December 2012)

a) Box and Whisker chart

b) All data points chart
Table 19  Variables Summary

<table>
<thead>
<tr>
<th>NICE TA and Date</th>
<th>TA192: Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (Jul-10).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>Gefitinib (mg) per 1,000 population</td>
</tr>
<tr>
<td>(numerator/denominator)</td>
<td></td>
</tr>
<tr>
<td>Level of Analysis</td>
<td>Area Team</td>
</tr>
<tr>
<td>Data type</td>
<td>Secondary care, AstraZeneca</td>
</tr>
</tbody>
</table>

The charts illustrate a steady increase in the mean over time. As uptake has increased over the three year period the data have become more dispersed around the mean. For some area teams the volumes of gefitinib used varied considerably quarter by quarter and less so for others. The overall picture is stable.

4.9.4 References


4.10 Multiple Myeloma - bortezomib, lenalidomide, thalidomide

4.10.1 Summary
Bortezomib as monotherapy is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation.

Bortezomib in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

Bortezomib in combination with dexamethasone, or with dexamethasone and thalidomide, is indicated for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. (SPC)

Lenalidomide in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

Lenalidomide is indicated for the treatment of patients with transfusion-dependent anaemia due to low or intermediate 1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. (SPC)

Thalidomide in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

Thalidomide is prescribed and dispensed according to the Thalidomide Pregnancy Prevention Programme. (SPC)

Bortezomib has been appraised by NICE as monotherapy for relapsed multiple myeloma (NICE TA guidance 129, 2007)¹:

Bortezomib monotherapy is recommended as an option for the treatment of progressive multiple myeloma in people 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:

- the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (that is, reduction in serum M protein of 50 per cent or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response) and

- the manufacturer rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a partial response (as defined above).
Bortezomib and thalidomide have been appraised by NICE for the first-line treatment of multiple myeloma (NICE TA guidance 228, 2011)²:

*Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate.*

*Bortezomib in combination with an alkylating agent 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 contraindications to thalidomide.

Lenalidomide has been appraised by NICE for the treatment of multiple myeloma in people who have received at least one prior therapy (NICE TA guidance 171, June 2009)³

*Lenalidomide in combination with dexamethasone is recommended, within its licensed indication, as an option for the treatment of multiple myeloma only in people who have received two or more prior therapies, with the following condition:*

- The drug cost of lenalidomide (excluding any related costs) for people who remain on treatment for more than 26 cycles (each of 28 days; normally a period of 2 years) will be met by the manufacturer.

### 4.10.2 Variation approach

These medicines have different treatment schedules making it difficult to estimate the volumes expected to be used and the number of patients treated. Also, bortezomib has a non-appraised use as a first line treatment for multiple myeloma in combination with melphalan. The proportional usage of bortezomib for the non-appraised indications could not be established.

A ‘use per patient’ approach has been adopted. The approach was agreed in discussion with the companies involved. This shows the combined number of cycles of treatment for each quarter.

Usage data for Lenalidomide and thalidomide was provided by Celgene, as the HPAI data was considered by the company to be incomplete. Data for Bortezomib is from HPAI.
4.10.3 Results

Figure 30  Number of treatment cycles for multiple myeloma drugs per 100,000 population aged 40 years and over. Secondary care prescribing trend, by Area Team (January 2010 – December 2012)

a) Box and Whisker chart

b) All data points chart
Table 20  Variables Summary

| NICE TA and Date | TA129: Bortezomib monotherapy for relapsed multiple myeloma (Oct -07).  
|                | TA228: Bortezomib and thalidomide for the first-line treatment of multiple myeloma (Jul -11)  
|                | TA171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (Jun -09)  
| Comparator (numerator/denominator) | Number of treatment cycles for multiple myeloma drugs per 100,000 population aged 40 years and over.  
| Level of Analysis | Area Team  
| Data type | Secondary care, Celgene data and HPAI  

The charts show an increase in use of these medicines over the time period.

4.10.4 References

2. TA228: Bortezomib and thalidomide for the first-line treatment of multiple myeloma, July 2011.
3. TA171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy, June 2009.
4.11 Myocardial infarction (persistent ST-segment elevation) – bivalirudin

4.11.1 Summary

Bivalirudin is indicated as an anticoagulant in adult patients undergoing percutaneous coronary intervention (PCI), including patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI.

Bivalirudin is also indicated for the treatment of adult patients with unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI) planned for urgent or early intervention.

Bivalirudin should be administered with aspirin and clopidogrel. (SPC)

NICE has appraised bivalirudin for the treatment of ST-segment-elevation myocardial infarction (NICE TA guidance 230, July 2011)\(^1\).

*Bivalirudin in combination with aspirin and clopidogrel is recommended for the treatment of adults with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention.*

4.11.2 Variation approach

Bivalirudin is one of a number of valid treatment options for this patient population and so the proportion of patients that would receive this medicine could not be established. The variation approach is not limited by this issue, and it enables comparison of changes over time and between organisations.

The variation approach adopts a ‘use per patient’ approach showing bivalirudin vials per 100,000 population\(^2\). Establishing other treatment options is complex and difficult to measure and compare on a ‘like for like’ basis. Therefore a ‘per cent use’ approach was ruled out.

The number of vials has been used as the numerator. Whilst a DDD is available it is likely that one vial is used per dose with any remaining drug being discarded. Therefore vials are a reasonable measure of use.

Per 100,000 population was chosen as the denominator. A STAR-PU weighting is not available for this medicine. It is not possible to define an age range in which bivalirudin is used.

The data used is from HPAI.
4.11.3 Results

Figure 31  Bivalirudin vials per 100,000 population\(^{(2)}\). Secondary care prescribing trend, by Area Team (January 2010 - December 2012)

a) Box and Whisker chart

b) All data points chart
Table 21  Variables Summary

<table>
<thead>
<tr>
<th>NICE TA and Date</th>
<th>TA230: Bivalirudin for the treatment of ST-segment-elevation myocardial infarction (Jul -11).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator (numerator/denominator)</td>
<td>Bivalirudin vials per 100,000 population</td>
</tr>
<tr>
<td>Level of Analysis</td>
<td>Area Team</td>
</tr>
<tr>
<td>Data type</td>
<td>Secondary care, HPAI</td>
</tr>
</tbody>
</table>

For the three year period covered data was available for 25 of the 27 area teams, with 10 having complete data for each of the 12 quarters. The TA was published in July 2011 and so compliance with the recommendations would be expected from November onwards. During 2012 more area teams increased their usage and so the mean increased.

### 4.11.4 References


4.12 Prevention of osteoporotic fractures - denosumab

4.12.1 Summary

Denosumab (60mg/ml) is indicated for:

- Treatment of osteoporosis in postmenopausal women at increased risk of fractures. Denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures.

- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (see section 3.1). In men with prostate cancer receiving hormone ablation, denosumab significantly reduces the risk of vertebral fractures. (SPC)

NICE has appraised Denosumab for the prevention of osteoporotic fractures in postmenopausal women (NICE TA guidance 204, Oct 2010). Denosumab is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures (see guidance).

Denosumab is recommended 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.

4.12.2 Variation approach

Denosumab was included with other appraised treatments for osteoporosis in section one of “Use of NICE appraised medicines in the NHS in England – 2010 and 2011” report. In this report denosumab is reported alone. A costing template was not produced for TA204 as the cost to the NHS was predicted to be less than £1 million per year. As a result no suitable data was available to estimate the proportion of patients that would receive denosumab. Also, the recommendations for treatment options with denosumab overlap with those for strontium ranelate.

A ‘use per patient’ approach has been adopted showing denosumab cost (£) per 1,000 female population aged 50 years and over. Denosumab is a treatment option and comparison with these other options was considered inappropriate as there are number of variables to consider e.g. increased risk, inability to comply with 1st line options. Therefore a ‘use per patient’ approach was preferred to a ‘per cent use’ approach.

The comparator chosen was cost (£) of prescribing of the brand/strength (60mg/ml pre-filled syringe) indicated for the prevention of osteoporotic fractures. Another preparation (70mg/ml, 1.7ml vial) is also available but for another indication. Cost is a proxy for volume of use and allows primary and secondary care data to be combined. Other measures are inappropriate as the treatment is administered on a 6 monthly basis.

Per 1,000 female population aged 50 years and over was chosen as the denominator. Whilst it is recognised that denosumab is also indicated for use in men, the population selected reflects the TA.
4.12.3 Results

Figure 32  Denosumab cost (£) per 1,000 female population aged 50 years and over\(^{(2)}\). Primary and secondary care prescribing trend, by Area Team (July 2010–December 2012) (*Cost based on 60mg strength)

a) Box and Whisker chart
b) All data points chart

![Graph showing the use of NICE appraised medicines in the NHS in England – 2012, experimental statistics](image)

Table 22  Variables Summary

<table>
<thead>
<tr>
<th>NICE TA and Date</th>
<th>TA204: Denosumab for the prevention of osteoporotic fractures in postmenopausal women (Oct-10).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>Denosumab cost (£) per 1,000 female population aged 50 years and over</td>
</tr>
<tr>
<td>(numerator/denominator)</td>
<td>* Cost based on 60mg strength indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fractures. This medicine is also available in 70mg dose for the reduction of bone damage in patients with bone metastases from solid tumours.</td>
</tr>
<tr>
<td>Level of Analysis</td>
<td>Area Team</td>
</tr>
<tr>
<td>Source of Prescribing</td>
<td>ePACT (Primary) and HPAI (secondary care)</td>
</tr>
</tbody>
</table>

The charts show substantial increase in use across the time period. Denosumab was being used by all area teams by January 2011.

4.12.4 References

1. TA204: Denosumab for the prevention of osteoporotic fractures in postmenopausal women, October 2010.

4.13 Prevention of osteoporotic fragility fractures - alendronate, etidronate, risedronate, raloxifene, strontium ranelate, and teriparatide

4.13.1 Summary

Alendronate is indicated for:

- Treatment of postmenopausal osteoporosis. Alendronic acid reduces the risk of vertebral and hip fractures.
- Treatment of osteoporosis in men at increased risk of fracture. A reduction in the incidence of vertebral, but not of non-vertebral fractures has been demonstrated.
- Prophylaxis of glucocorticoid-induced osteoporosis. (SPC)

Etidronate is indicated for:

- Treatment of osteoporosis and prevention of bone loss in postmenopausal women considered at risk of developing osteoporosis. Etidronate PMO is particularly indicated in patients who are unable or unwilling to take oestrogen replacement therapy.
- Etidronate PMO is also indicated for the prevention and treatment of corticosteroid induced osteoporosis. (SPC)

Risedronate is indicated for:

- Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures.
- Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures.
- Treatment of osteoporosis in men at high risk of fractures. (SPC)

Raloxifene is indicated for the treatment and prevention of osteoporosis in postmenopausal women. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated. (SPC)

Strontium ranelate is indicated for:

- Treatment of severe osteoporosis in postmenopausal women at high risk of fracture to reduce the risk of vertebral and hip fractures.
- Treatment of severe osteoporosis in adult men at increased risk of fracture. (SPC)

Teriparatide is indicated in adults for the treatment of:

- Osteoporosis in postmenopausal women and in men at increased risk of fracture. In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures has been demonstrated.
- Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture. (SPC)
NICE has appraised these drugs for primary prevention of osteoporotic fragility fractures in postmenopausal women (NICE TA guidance 160, 2008)

*Alendronate is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in the following groups (see guidance).*

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

*Strontium ranelate is recommended as an alternative treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women (see guidance).*

*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 the secondary prevention of osteoporotic fragility fractures in postmenopausal women (NICE TA guidance 161, 2008)

*Alendronate is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are confirmed to have osteoporosis (see guidance).*

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

*Strontium ranelate and raloxifene are recommended as alternative treatment options for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (see guidance).*

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

### 4.13.2 Variation approach

Alendronate, etidronate, risedronate, raloxifene, strontium ranelate, teriparatide and denosumab were included in section one of “Use of NICE appraised medicines in the NHS in England – 2010 and 2011” report. In this year’s report these medicines have been selected for the variation approach as their use in therapy is now well established and it was felt that it would be of more value for readers to show variation over time. This approach may assist in identifying those localities where there may be issues of appropriately identifying individuals for whom osteoporotic fracture prevention with these medicines is an option.

A ‘use per patient’ approach has been adopted showing items of alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide per head of female population aged 50 years and over. All treatment options, (with the exception of denosumab which is covered separately), are included in the TA. The majority of prescribing of these drugs is in primary care except for teriparatide, for which use in secondary care is also shown.

Items has been chosen as the numerator. At Area Team level items is likely to as robust a measure as DDDs.

Per head of female population aged 50 years and over has been chosen as the denominator. Whilst it is recognised that denosumab is also indicated for use in men, the population selected reflects the NICE TA.
4.13.3 Results

Figure 33  Items of alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide per head of female population aged 50 years and over. Primary care prescribing trend, by Area Team (January 10 – December 12)

a) Box and Whisker chart

b) All data points chart
Figure 34  Teriparatide pens per 100,000 female population aged 50 years and over.  Secondary care prescribing trend by Area Team (January 10 – December 12)

a) Box and Whisker chart

b) All data points chart
Table 23 Variables Summary

<table>
<thead>
<tr>
<th>NICE TA and Date</th>
<th>TA160: Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (amended) (Oct-08, amended Jan-10 and Jan–11)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TA161: Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (amended) (Oct–08, amended Jan–10 and Jan-11)</td>
</tr>
<tr>
<td>Comparator (numerator/denominator)</td>
<td>Figure 33: Items per head of female population aged 50 years and over</td>
</tr>
<tr>
<td>Level of Analysis</td>
<td>Area Team</td>
</tr>
<tr>
<td>Data type</td>
<td>Figure 33: Primary care, ePACT</td>
</tr>
</tbody>
</table>

Figure 33a and b show an overall increase in prescribing of these medicines over time. Consistently higher levels of prescribing are seen by one area team. Volumes of teriparatide are relatively low as illustrated by Figure 34a and b. Higher levels of prescribing are seen for four or five area teams. For the majority of area teams prescribing levels are stable. However, increased volatility is seen for those area teams where there is higher usage.

4.13.4 References


4.14 Prevention of stroke and systemic embolism in atrial fibrillation – dabigatran etexilate and rivaroxaban

4.14.1 Summary

Dabigatran is indicated for:

- **Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery**

- **Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:** Previous stroke, transient ischemic attack, or systemic embolism (SEE); Left ventricular ejection fraction < 40% per cent; Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2; Age ≥ 75 years and; Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension (SPC).

Rivaroxaban is indicated for:

- **Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.**

- **Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (SPC).**

NICE has appraised dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (NICE TA guidance 249, 2012):

**Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more of the following risk factors:**

- previous stroke, transient ischaemic attack or systemic embolism
- left ventricular ejection fraction below 40 per cent
- symptomatic heart failure of New York Heart Association (NYHA) class 2 or above
- 75 years or older
- 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension.

Dabigatran etexilate has also been appraised by NICE for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (NICE TA guidance 157, 2008).
NICE has appraised rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation (NICE TA guidance 256, 2012):

**Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more risk factors such as:****

- congestive heart failure
- hypertension
- age 75 years or older
- diabetes mellitus
- prior stroke or transient ischaemic attack.

NICE has also appraised rivaroxaban for:

- prevention of venous thromboembolism after total hip or total knee replacement in adults (NICE TA guidance 170, 2009).
- treating pulmonary embolism and preventing recurrent venous thromboembolism (NICE TA guidance 287, 2013 – note that this recommended indication is outside the time period covered by this report).

Apixaban was appraised by NICE for the prevention of stroke and systemic embolism in people with nonvalvular atrial fibrillation in February 2013. Given the timing of the TA this recommended indication is outside the time period covered by this report (NICE TA guidance 275).

### 4.14.2 Variation approach

Dabigatran etexilate and rivaroxaban were appraised by NICE for the prevention of stroke and systemic embolism in people with atrial fibrillation during 2012. These medicines have also been appraised by NICE for the prevention of thromboembolism following hip or knee replacement (see section 4.15). A number of other valid treatment options are available for the prevention of stroke and systemic embolism in people with atrial fibrillation. Prescribing data by diagnosis is not available and so proportional usage by indication could not be established to support the development of an estimate of eligible patients. The variation approach is not limited by these issues and it enables comparison between organisations and shows changes over time.

Figure 39 shows relative use of the newer anti-coagulants and warfarin in primary care. The data is reported as number of items. However, it should be noted that many patients treated with warfarin will receive up to three prescription items at each clinic visit as an individual patient’s dose may require up to three different strengths of tablets to allow them to alter dose in response to monitoring. Therefore use of dabigatran etexilate and rivaroxaban instead of warfarin could replace up to three items of warfarin.

The variation approach adopts a ‘per cent use’ approach showing items of dabigatran etexilate and rivaroxaban. The use of dabigatran etexilate and rivaroxaban are alternative options to warfarin and therefore this approach allows for a measure of the uptake of these drugs in comparison with warfarin.
Items for dabigatran, rivaroxaban and warfarin has been chosen for the numerator and denominator. Whilst DDDs are available for all three drugs included in the comparator, the DDD for warfarin (7.5mg) more reflects use in loading doses/secondary care and is likely to be higher than in use in primary care. Use of DDDs could therefore further distort the proportional use of warfarin.

4.14.3 Results

Figure 35 Items of dabigatran etexilate and rivaroxaban as a proportion of items for dabigatran, rivaroxaban and warfarin. Primary care prescribing trend, by Area Team (January 2012 – December 2012)

a) Box and Whisker chart
Use of NICE appraised medicines in the NHS in England – 2012, experimental statistics

b) All data points chart

![Data Points Chart]

Table 24  Variables Summary

| NICE TA and Date (only includes TAs relating to dabigatran etexilate and rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation) | TA249: Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (Mar-12).
| TA256: Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation (May-12).
| TA261: Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism (Jul-12). |

| Comparator (numerator/denominator) | Items of dabigatran etexilate and rivaroxaban as a proportion of items for dabigatran etexilate, rivaroxaban and warfarin. |

| Level of Analysis | Area Team |
| Data type | Primary care, ePACT |

Four quarters of data are shown, due to the recent appraisal. The NHS has three months following publication of a TA to comply with the recommendations. Proportional uptake of these medicines has been compared using prescription items. Different strengths of warfarin tablets are often combined to achieve a daily maintenance dose and so more than one warfarin item may be prescribed per patient. This may give the impression of proportionately higher use of warfarin than compared to dabigatran etexilate and rivaroxaban.

Figure 37 (in section 4.15.3) shows the increase in DDDs use of dabigatran, rivaroxaban and apixaban in primary and secondary care from January 2010 to December 2012.
4.14.4 References

1. TA249: Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation, March 2012.


4. TA170: Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults, April 2009.


6. TA287: Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism, June 2013.
4.15 Prevention of venous thromboembolism after hip or knee replacement surgery - dabigatran etexilate, apixaban and rivaroxaban

4.15.1 Summary

Dabigatran is indicated for:

- **Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery**
- **Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:** Previous stroke, transient ischemic attack, or systemic embolism (SEE); Left ventricular ejection fraction < 40 per cent; Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2; Age ≥ 75 years and; Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension. (SPC)

Apixaban is indicated for:

- **Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.**
- **Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II). (SPC)**

Rivaroxaban is indicated for:

- **Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.**
- **Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (SPC)**

NICE has appraised dabigatran for the prevention of venous thromboembolism after total hip or knee replacement surgery (NICE TA guidance 157, 2008):

*Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery.*

Dabigatran has also been appraised by NICE for the prevention of stroke and systemic embolism in atrial fibrillation (NICE TA guidance 249, 2012).

Apixaban has been appraised by NICE for the prevention of thromboembolism after elective total hip or knee replacement in adults (NICE TA guidance 245, 2012):

*Apixaban is recommended as an option for the prevention of venous thromboembolism in adults after elective total hip or knee replacement surgery.*
Apixaban has also been appraised by NICE for the prevention of stroke and systemic embolism in people with nonvalvular atrial fibrillation (NICE TA guidance 275, 2013)

Rivaroxaban has been appraised by NICE for the prevention of venous thromboembolism after total hip or knee replacement in adults (NICE TA guidance 170, 2009):

*Rivaroxaban, within its marketing authorisation, is recommended 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 also appraised rivaroxaban for:

- the prevention of stroke and systemic embolism in people with atrial fibrillation (NICE TA guidance 256, 2012)
- the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism (NICE TA guidance 261, 2012)
- treating pulmonary embolism and preventing recurrent venous thromboembolism (NICE TA guidance 287, 2013)

### 4.15.2 Variation approach

A number of valid treatment options are available for the prevention of thromboembolism following hip or knee replacement. The proportion of patients that would receive each medicine could not be established. This limitation could not be overcome and so an estimate of the number of eligible patients and the likely volume of medicine to be consumed could not be developed with sufficient certainty. The variation approach enables comparison of changes over time and between organisations and is not limited by this issue.

A 'use per patient' approach has been adopted showing DDDs of dabigatran etexilate, apixaban and rivaroxaban by area team population. A ‘per cent use’ approach is difficult for secondary care data as the selection and measurement of other treatment options (denominator) is complex.

DDDS of dabigatran etexilate, apixaban and rivaroxaban has been chosen as the numerator. It is not possible to measure 'items' in secondary care. The costs of the drugs are different and therefore not appropriate to use in a comparator that includes all three drugs.

Population (Area team) has been chosen as the denominator. It is not possible to define and age range where these drugs are likely to be used.

Figure 36 reports use (DDDs) in hospital trusts by area team population. The comparator reports secondary care data only as the use of these drugs for the indications recommended by the TA will be initiated in hospital. It has been assumed that following hip or knee replacement surgery either the full course will be administered in hospital or the remainder of the treatment course provided on discharge. This allows the comparator to show variation in uptake in secondary care and also differentiate between other indications for longer term use of these medicines for which prescribing is likely to be also undertaken in primary care.
4.15.3 Results

Figure 36 Defined daily doses of dabigatran etexilate, apixaban and rivaroxaban by area team population. Secondary care prescribing trend, (January 2010 – December 2012)

a) Box and Whisker chart
Use of NICE appraised medicines in the NHS in England – 2012, experimental statistics

b) All data points chart

![Graph showing usage of NICE appraised medicines over time]

Table 25  Variables Summary

| NICE TA and Date | TA157: Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (Sep-08).
|                 | TA170: Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (Apr-09).
|                 | TA245: Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults (Jan-12).
| Comparator (numerator/denominator) | DDDs by area team population
| Level of Analysis | Area Team
| Data type | Secondary care, HPAI

Figure 36 illustrates an increase in the mean during 2010 and 2012.

Figure 37 shows England usage in DDDs of dabigatran, rivaroxaban and apixaban in both primary and secondary care by quarter, using data from ePACT and HPAI.
Figure 37 shows an increase in the total use of these drugs over time, which has accelerated during 2012.

4.15.4 References
2. TA249: Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation, March 2012.
5. TA170: Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults, April 2009.
8. TA287: Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism, June 2013.
4.16 Prucalopride

4.16.1 Summary

Prucalopride is indicated for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. (SPC)

NICE has appraised prucalopride for the treatment of chronic constipation in women (NICE TA guidance 211, 2010).

Prucalopride is recommended 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 six months, has failed to provide adequate relief and invasive treatment for constipation is being considered.

4.16.2 Variation approach

Prucalopride was included in section one of “Use of NICE appraised medicines in the NHS in England – 2010 and 2011” report. In that report it was estimated that actual usage was 89 per cent lower than expected for 2011. This raised concerns about the calculation of the eligible population. Prucalopride is recommended as a treatment option for chronic constipation in women for whom at least two laxatives from different classes and six months treatment have failed. The proportion of women who undergo treatment with more than two types of laxatives before being considered for treatment with prucalopride is not known. This raises on-going concerns about the accuracy of the original estimate. The manufacturer felt that there should be a clearer definition for those patients for whom prucalopride is not thought to be effective before continuation of treatment is reviewed. The variation approach is not constrained by these issues.

A ‘use per patient’ approach has been adopted showing prucalopride tablets per 10,000 female population aged 18 years and over. Other treatment options are numerous, prescribed for all ages and are complex to measure across primary and secondary. Also prucalopride is recommended only when other treatment options have been ineffective and in a specific population and it’s use is low. Therefore a ‘per cent use’ approach was considered inappropriate.

Tablets have been used as the numerator. The DDD is 2mg which reflects daily use in the majority of patients (2mg daily) the recommended starting dose for patients aged 65 years and over is 1mg, increased if necessary to 2mg (SPC). Using tablets allows for any variation in doses prescribed.

Per 10,000 female population aged 18 years and over has been selected as the denominator as this is specific to the recommendations in the NICE TA 211 and the manufacturers SPC.
4.16.3 Results

Figure 38  Prucalopride tablets per 10,000 female population aged 18 years and over\(^{(2)}\). Primary and secondary care prescribing trend, by Area Team (April 2010 – December 2012)

a) Box and Whisker chart

![Box and Whisker chart]

b) All data points chart

![All data points chart]
Table 26 Variables Summary

<table>
<thead>
<tr>
<th>NICE TA and Date</th>
<th>TA 211: Prucalopride for the treatment of chronic constipation in women (Dec-10).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator (numerator/denominator)</td>
<td>Tablets per 10,000 female population aged 18 years and over</td>
</tr>
<tr>
<td>Level of Analysis</td>
<td>Area Team</td>
</tr>
<tr>
<td>Data type</td>
<td>ePACT (Primary) and HPAI (secondary care)</td>
</tr>
</tbody>
</table>

The mean use of prucalopride has increased over time. Consistently higher usage has been seen by one area team. Rates of growth in the uptake of this medicine have remained consistent with dispersion around the mean increasing with increased uptake.

4.16.4 References
4.17 Short-term management of insomnia - zaleplon, zolpidem and zopiclone

4.17.1 Summary

Zaleplon is indicated for the treatment of patients with insomnia who have difficulty falling asleep. It is indicated only when the disorder is severe, disabling or subjecting the individual to extreme distress. (SPC)

Zolpidem is indicated for the short-term treatment of insomnia in situations where the insomnia is debilitating or is causing severe distress for the patient. (SPC)

Zopiclone is indicated for short term treatment of insomnia, including difficulties in falling asleep, nocturnal awakening and early awakening, transient, situational or chronic insomnia, and insomnia secondary to psychiatric disturbances, in situations where the insomnia is debilitating or is causing severe distress for the patient. Long term continuous use is not recommended. A course of treatment should employ the lowest effective dose. (SPC)

Given the risks associated with the use of benzodiazepines, patients should be prescribed the lowest effective dose for the shortest time possible. Maximum duration of treatment should be 4 weeks, including the dose-tapering phase (MHRA).

Zaleplon, zolpidem and zopiclone have been appraised by NICE for the short term management of severe insomnia interfering with normal daily life (NICE TA 77, 2004):1

When, after due consideration of the use of nonpharmacological measures, hypnotic drug therapy is considered appropriate for the management of severe insomnia interfering with normal daily life, it is recommended that hypnotics should be prescribed for short periods of time only, in strict accordance with their licensed indications.

It is recommended that, because of the lack of compelling evidence to distinguish between zaleplon, zolpidem, zopiclone or the shorter-acting benzodiazepine hypnotics, the drug with the lowest purchase cost (taking into account daily required dose and product price per dose) should be prescribed.

It is recommended that switching from one of these hypnotics to another should only occur if a patient experiences adverse effects considered to be directly related to a specific agent. These are the only circumstances in which the drugs with the higher acquisition costs are recommended.

Patients who have not responded to one of these hypnotic drugs should not be prescribed any of the others.

4.17.2 Variation approach

These medicines were not included in the “Use of NICE appraised medicines in the NHS in England – 2010 and 2011” report. This was because a number of factors have affected the use of these medicines, which invalidates the original estimates. These factors include:

- temazepam changed status to become a Schedule 3 Controlled Drug, which led to reduced use of temazepam and increased use of alternative medicines18
- hypnotics and anxiolytics are also used in the management of opiate misuse

18 For more information see Prescriptions Dispensed in the Community 2002-2012, HSCIC (available at: http://www.hscic.gov.uk/catalogue/PUB11291)
The variation approach was considered to provide a clearer understanding of prescribing for hypnotics. A 'use per patient' and a 'per cent use' approach have been adopted. Whilst the NICE TA guidance (77) specifically considers zaleplon, zolpidem and zopiclone (Z drugs), the TA also recommends non-pharmacological treatment and also the option of using shorter acting (hypnotic) benzodiazepines with choice based on purchase price. Therefore it is appropriate to present variation as both use of all drugs per patient and use of Z drugs as a proportion of all drugs used for insomnia. Figure 39 shows use of these medicines by weighted population over the last 12 quarters. Figure 40 shows the use of zaleplon, zolpidem and zopiclone as a proportion of all prescribing of hypnotics. Primary care data is used for both as the majority of prescribing is undertaken in primary care.

Figure 39 shows average daily quantities (ADQ) of hypnotic benzodiazepines and Z-drugs per STAR-PU². This comparator is a QIPP comparator. ADQs have been chosen as the numerator as they provide a more accurate measure of use given that the quantity prescribed per item may vary. STAR-PUs (ADQ based) specific to the drugs included in the numerator have been chosen as the denominator. This applies age and sex weightings to be applied to the population data.

Figure 40 shows the number of Z-drug items as a percentage of items for hypnotic benzodiazepines and Z-drugs. Items for zaleplon, zolpidem and zopiclone has been chosen as the numerator. In this case items rather than DDDs are preferred as quantity per prescription item and dose prescribed will not distort the proportional use. Items for Z drugs and all benzodiazepines indicated for use as hypnotics have been chosen as the denominator. Items rather than DDDs are preferred as quantity per prescription item and dose prescribed will not distort the proportional use.
4.17.3 Results

Figure 39  Average daily quantities (ADQ) of hypnotic benzodiazepines and Z-drugs per STAR-PU(2). Primary care prescribing trend, by Clinical Commissioning Group. (January 2010 - December 2012)

(a) Box and Whisker chart
b) All data points chart
Figure 40  Number of Z-drug items as a percentage of items for hypnotic benzodiazepines and Z-drugs. Primary care prescribing trend, by Clinical Commissioning Group (January 2010 - December 2012)

a) Box and Whisker chart

b) All data points chart
Table 27  Variables Summary

<table>
<thead>
<tr>
<th>NICE TA and Date</th>
<th>Comparator (numerator/denominator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA77: Guidance on the use of Zaleplon, Zolpidem, and Zopiclone for the short-term management of insomnia (April 07).</td>
<td>Figure 39: Average daily quantities (ADQ) for hypnotic benzodiazepines and Z Drugs per STAR-PU. Figure 40: Number of Z-drug items as a percentage of items for hypnotic benzodiazepines and Z-drugs.</td>
</tr>
</tbody>
</table>

Level of Analysis: Clinical Commissioning Group
Data type: Primary care, ePACT

Figure 41 shows the number of items for the ‘Z’ Drugs (Zaleplon, Zolpidem Tartrate, Zopiclone), Benzodiazepines (Flurazepam Hydrochloride, Loprazolam Mesilate, Lormetazepam, Nitrazepam, Temazepam) and Other Hypnotics (Chloral Hydrate, Clomethiazole, Clomethiazole Edisilate, Cloral Betaine, Melatonin, Other Hypnotic Preps, Sodium Bromide, Sodium Oxybate, Triclofos Sodium) using data from ePACT.

Figure 39a and b show ADQs per STAR-PU for zaleplon, zolpidem and zopiclone and the hypnotic benzodiazepines. These show a decrease in mean levels of prescribing of hypnotic benzodiazepines and Z-drugs over time. This is the expected pattern and reflects national policy to reduce the inappropriate use of hypnotic agents.
Figure 40a and b show an increase in the mean over time. This reflects an increase in the proportion of hypnotic medicines which are zaleplon, zolpidem or zopiclone. This is also shown in Figure 41.

4.17.4 References


4.18 Smoking cessation - varenicline

4.18.1 Summary

Varenicline is indicated for smoking cessation in adults. (SPC)

Varenicline has been appraised by NICE as an aid for smoking cessation (NICE TA 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.**

4.18.2 Variation approach

There are three options which can be prescribed to support adults who are over 18 years and who wish to stop smoking – nicotine replacement therapy (NRT), bupropion or varenicline. The NICE Clinical Knowledge Summary provides a table which compares these options.

The NICE public health guidance 10 supports use of all three possible options and explicitly says, “Do not favour one medication over another. The clinician and patient should choose the one that seems most likely to succeed.”

Varenicline was included as an estimate in section one of the ‘use of NICE appraised medicines, 2010 and 2011’ report. However, there are problems establishing a value for the proportion of quitters using this medicine rather than the alternatives. The variation approach can be used to show use of varenicline compared to all nicotine dependence medicines as defined in the table shown below the charts.

A ‘per cent use’ approach has been adopted showing items of varenicline as a proportion of all nicotine dependence medicines. As varenicline is a treatment option (see above) it is appropriate to measure uptake as a proportion of all options. Items of varenicline has been chosen as the numerator. Items for all drugs prescribed for nicotine dependence (BNF 4.10.2) has been chosen as the numerator. i.e. Nicotine, bupropion and varenicline. Note that these drugs, particularly nicotine replacement treatments, may be supplied in other routes not captured in primary care prescribing data (see below).
4.18.3 Results

Figure 42  Items of varenicline as a proportion of all nicotine dependence medicines. Primary care prescribing trend by Area Team (January 2010 - December 2012)

a) Box and Whisker chart

b) All data points chart
Table 28  Variables Summary

<table>
<thead>
<tr>
<th>NICE TA and Date</th>
<th>TA123: Varenicline for smoking cessation (July-07)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>Varenicline as a proportion of all nicotine dependence medicines</td>
</tr>
<tr>
<td>(numerator/denominator)</td>
<td></td>
</tr>
<tr>
<td>Level of Analysis</td>
<td>Area Team</td>
</tr>
<tr>
<td>Data type</td>
<td>Primary care, ePACT</td>
</tr>
</tbody>
</table>

The chart below shows the number of items for varenicline and other nicotine dependence medicines (Bupropion Hydrochloride, Nicotine,) using data from ePACT.

Figure 43  Number of items for varenicline and other nicotine dependence medicines (July 2008 - December 2012)

The data shows marked seasonal variation in the use of these products. Varenicline and bupropion are prescription only medicines, but can be supplied by smoking cessation clinics. Nicotine replacement products can be purchased over the counter. Therefore the values shown here will be an underestimate of all use, and some variation will relate to how local services are structured and how medicines are supplied.

4.18.4 References
5. PH10 Smoking cessation services, February 2008.
## 5 Future Developments

This report has made progress on issues previously identified, however these issues are complex to resolve and further work is required.

Areas to be considered for future reports, subject to sufficient resources include:

- Continuing improvements in data collection and reporting at both national and sub-national levels.
- The potential of new sources of information, for example the Systemic Anti-Cancer Therapy (SACT) data set
- Developments in the provision and recording of data relating to the supply of medicines outside the hospital pharmacy department, such as homecare and outsourcing.
- Further development and review of estimates, particularly for those medicines which were appraised soon after launch or were reviewed several years ago.
- Despite significant work it was not possible in this report to derive a sufficiently robust estimate for Hepatitis C medicines. This is recognised as a clinical area with particular difficulties in ensuring all eligible patients are treated. Public Health England have agreed to contribute to further work on these medicines.
- Reporting on levels of confidence in the estimates. Following the last report, the Government Statistical Service (GSS) have made recommendations to include more measures around the robustness of estimates. The development of the GSS recommendations would require substantial resource which has not been available for this report.
- Reviewing additional medicines for suitability of reporting using the variation approach.
- Reviewing the comparators (numerators and denominators) used for reporting variation.
- Reviewing further ways of showing statistical variation in a manner that would be user friendly.
- The PPRS has been renewed. The PPRS 2014 has continued the commitment to report comparative use of medicines positively appraised by NICE. DH, NHS England and the industry will work together to deliver activities to meet this commitment.

This report has experimental status and feedback from readers 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.
6 Sources and Definitions

6.1 Data Sources

6.1.1 Hospital Prescribing Audit Index (HPAI) database

IMS Health collect data from pharmacies in hospital trusts across the UK, to produce the Hospital Pharmacy Audit Index (HPAI). The data relating to England has been made available by IMS Health. IMS Health releases data on a regular basis. Each IMS dataset includes data for 24 months and may include updates to earlier data.

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 AT data used in the report may be an underestimate if any trusts within a AT do not contribute data.

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 homecare 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. Information from the NHS Commercial Medicines Unit estimate that the cost of homecare in England exceeds £1.5 billion per year. 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.

Not all Mental Health Trusts use hospital pharmacies and so some of their activity will not be recorded.

The prices used in the HPAI are the published prices from the Drug Tariff and other standard price lists. This is not a true reflection of the actual expenditure by hospitals as many purchases are made on contract with individual manufacturers or wholesalers at lower prices.

The HPAI includes no information taken directly from private hospitals, so excludes treatments for patients receiving NHS care in private hospitals. The data used in this report will however include usage in private wards within NHS hospitals, or where the NHS hospital supplies a private hospital.

Where the data received can be linked to a valid UK pack, clinical trial usage will be incorporated. This is not always possible as clinical trial packs may not be issued from or recorded within the hospital pharmacy system.

Certain types of drug, notably some cytotoxics and intravenous nutrition, are prepared in aseptic conditions. This may be carried out at a separate site by an outside contractor. IMS are unable to collect this data from one site in England. If the data relate to issues from an
aseptic unit, it is not always possible to determine the quantity of drugs used. In such instances an average quantity is substituted.

6.1.2 Primary Care (ePACT)

This information is obtained from the Prescribing Analysis and Cost (PACT) system, which covers prescriptions prescribed by GP practices in England and dispensed in the community in the UK. Prescriptions written in England but dispensed outside England are included.

Prescriptions written in hospitals or clinics that are dispensed in the community, prescriptions dispensed in hospitals and private prescriptions are not included in PACT data. The data in this report have been provided by the Prescription Services Division of the BSA, which has arranged the data by month and by the AT and CCG of the prescriber. This data are widely considered to have high levels of accuracy and completeness.

6.1.3 Prescriptions issued in hospitals and dispensed in the community – “FP10HP”

This route of medicine supply is sometimes referred to FP10HP as, formerly, hospital prescribers used a prescription form, with this reference name, which was similar to those used routinely in primary care, the FP10. The forms now used by hospital prescribers have the same reference name as those used in primary care and are differentiated by the cost centre details overprinted on the form and the title Hospital Prescriber and HP at the top of the prescribing section of the form. The term FP10HP is continued to be used in this report as a convenient way of referring to this method where the prescription is written by a hospital prescriber when it is intended that the patient will have the prescription dispensed in the community. The cost of the prescription is charged to the hospital. The data in this report have been provided by the Prescription Services Division of the BSA, which has arranged the data by month and by the AT and CCG of the prescriber.

6.1.4 Data from Companies

Pharmaceutical companies were invited to contribute data where they felt that the data available to the HSCIC was not suitable. Several companies contributed data as described in the relevant parts of section 3 and 4.

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

6.1.5 Population Data

England population estimates were obtained from the Office for National Statistics (ONS) mid 2011 estimated resident population by single year of age and sex, and by . See: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-england-and-wales/mid-2011--2011-census-based-/index.html
6.2 Methods of medicine supply - routes and data collection

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 29 below.

<table>
<thead>
<tr>
<th>Route</th>
<th>Method of medicine supply</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 Division of NHSBSA)</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 oral products)</td>
<td>Yes if dispensed in England (List B from Prescription Services Division of NHSBSA)</td>
<td>No (unlikely to be relevant)</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 (FP10HP/Hospital ePACT from Prescription Services Division of NHSBSA)</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 (unlikely to be relevant)</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 system</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>
<tr>
<td>M</td>
<td>Medicines administered in ambulances</td>
<td>No</td>
<td>Only if provided by hospital pharmacy and in HPAI data</td>
</tr>
</tbody>
</table>
6.3 Definitions / Glossary

Area Team (AT)
NHS England ATs are responsible for commissioning all primary care services (including GP and dental services and a wide range of pharmacy and optician services) as well as some specialised hospital services. They also have responsibility for co-ordinating and shaping healthcare across their area.

ASTRO-PU weightings
ASTRO-PU stands for Age, Sex and Temporary Resident Originated Prescribing Units. This weighting is designed to weight individual practice populations for age, sex and temporary residents to allow for better comparison of prescribing patterns. These figures are based on the cost of prescribing across all therapeutic areas.

Average Daily Quantity (ADQ)
This a measure of prescribing volume based on prescribing behaviour in England. It represents the assumed average maintenance dose per day for a drug used for its main indication in adults. The ADQ is not a recommended dose but an analytical unit to compare prescribing activity.

Clinical Commissioning Groups (CCG)
CCGs commission most of the hospital and community NHS services in the local areas for which they are responsible. CCGs are overseen by NHS England. All GP practices now belong to a CCG, and the groups also include other health professionals, such as nurses.

Clinical Guideline (CG)
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. See http://guidance.nice.org.uk/Type for further information.

Defined Daily Dose (DDD)
The World Health organisation define this as the assumed average maintenance dose per day for a drug used for its main indication in adults.

ePACT
Data provided by Prescription Services (part of the NHS BSA) covering prescriptions prescribed by GP practices in England and dispensed in the community in the UK.

FP10HP
Data provided by Prescription Services (part of the NHS BSA) covering prescriptions written in secondary care when it is intended that the patient will have the prescription dispensed in the community.

Hospital Pharmacy Audit Index (HPAI)
HPAI, 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.
Issue
When a hospital pharmacy supplies medication to a ward or operating theatre or to a patient who is being discharged. This supply is usually termed an ‘issue’.

Items
Prescriptions are written on a prescription form known as a FP10. Each single item written on the form is counted as a prescription item. The term “prescribed” is used throughout this publication to mean items which were both prescribed and dispensed.

Medicines and Healthcare Products Regulatory Agency (MHRA)
The MHRA is responsible for regulating all medicines and medical devices in the UK by ensuring they work and are acceptably safe.

Net Ingredient Cost (NIC)
This is the basic price of a drug, i.e. the price listed in the national Drug Tariff or in standard price lists. NIC is used in Prescription Services reports and other analyses, as it standardises cost throughout prescribing nationally. The actual price paid by the NHS takes into account any discounts.

STAR-PU weightings
There are differences in the age and sex of patients who are prescribed drugs in specific therapeutic groups, for instance dementia drugs will be represented in older age brackets. STAR-PUs (Specific Therapeutic Group Age-sex weightings Related Prescribing Units) allow you to make comparisons within a specific therapeutic group by taking into account the types of people who will be receiving that treatment. They have been developed along similar lines to the ASTRO-PU but based on costs within therapeutic groups.

Summaries of Product Characteristics (SPC)
A SPC tells healthcare professionals, such as doctors, pharmacists and nurses, how to prescribe and use a medicine correctly. A SPC is based on clinical trials that a pharmaceutical company has carried out, and gives information about dose, use and possible side effects.

Technology Appraisal (TA)
TAs are 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. Recommendations are based on a review of clinical and economic evidence. See http://guidance.nice.org.uk/Type for further information.
7 Further Information

The following provides information about other publications which may be of interest to the readers of this publication.

7.1 Other HSCIC Publications

7.1.1 NICE Technology Appraisals in the NHS in England, Innovation Scorecard

The Innovation Health and Wealth paper, published by DH in December 2011, set out plans to support development and adoption of innovation in the NHS. One of the actions in this paper is to drive compliance with TAs by the publication of information relating to levels of compliance and variation at a local level. The HSCIC was requested to develop and publish a scorecard on behalf of DH and the NHS England. There is no central collection of data to directly support this, nor is data on the number of patients treated available centrally. Therefore this is an experimental publication, which presents available data from a range of sources and requests comments and suggestions from readers to support future development of appropriate datasets. See http://www.hscic.gov.uk/catalogue/PUB11832

7.1.2 Prescription Cost Analysis

Prescription Cost Analysis (PCA) provides details of the number of items and the net ingredient cost of all prescriptions dispensed in the community in England. The drugs dispensed are listed by British National Formulary (BNF) therapeutic class. See www.hscic.gov.uk/pubs/prescostanalysiseng2012

7.1.3 Prescriptions Dispensed in the Community

This Prescriptions Dispensed in the Community publication uses the PCA data and presents a summary of prescriptions dispensed in the community by community pharmacists, appliance contractors and dispensing doctors in England. The bulletin highlights recent changes and the main trends between 2002 and 2012. See www.hscic.gov.uk/pubs/presdisp0212

7.1.4 Hospital Prescribing

This report compares prescribing expenditure between primary and secondary care in total and for selected areas, including medicines positively appraised by NICE. The 2012 report analysed anti-bacterial drugs (BNF Section 5.1) in more detail. See http://www.hscic.gov.uk/pubs/hospre12

7.1.5 Prescribing for Diabetes


7.1.6 HSCIC HES data

Information about those admitted to hospital can be found in Hospital Episode Statistics (HES). HES is a data warehouse containing details of all admissions, outpatient appointments and Accident and Emergency attendances at NHS hospitals in England. This data is collected during a patient's time at hospital and is submitted to allow hospitals to be paid for the care they deliver. HES data is designed to enable secondary use, that is use for non-clinical purposes, of this administrative data. It is a records-based system that covers all NHS trusts in England, including acute hospitals, primary care trusts and mental health trusts. See http://www.hscic.gov.uk/hes.
7.1.7 Clinical Audits
The HSCIC are commissioned to run audits by a number of organisations including the Healthcare Quality Improvement Partnership, British Heart Foundation and Royal College of Surgeons. The audit results allow national health organisations to compare their performance against specific standards and national trends, enabling them to deliver better care for their patients. Audits cover a range of clinical areas including diabetes, lung cancer, and cardiac rehabilitation. See http://www.hscic.gov.uk/clinicalaudits.

7.2 Non HSCIC information
Please note that the HSCIC is not responsible for external organisations or links.

7.2.1 Equivalent statistical publications in other UK countries
The statistics used in this publication are based on figures for England. The HSCIC does not collect or supply similar figures for the other UK countries.

The Devolved Administrations publish information on prescribing in their countries. For further information please contact:

<table>
<thead>
<tr>
<th>Wales</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Welsh Assembly Government</td>
<td>Public enquiries: 029 2082 5050</td>
</tr>
<tr>
<td>Statistical Directorate</td>
<td>E-mail: <a href="mailto:stats.healthinfo@wales.gsi.gov.uk">stats.healthinfo@wales.gsi.gov.uk</a></td>
</tr>
<tr>
<td>Cathays Park</td>
<td>Website: <a href="http://www.wales.gov.uk/statistics">www.wales.gov.uk/statistics</a></td>
</tr>
<tr>
<td>Cardiff</td>
<td></td>
</tr>
<tr>
<td>CF10 3NQ</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scotland</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Information Services Division,</td>
<td>Customer Support Desk: 0131 275 7777</td>
</tr>
<tr>
<td>NHS National Services</td>
<td>Email: <a href="mailto:nss.csd@nhs.net">nss.csd@nhs.net</a></td>
</tr>
<tr>
<td>Scotland</td>
<td>Website: <a href="http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/">http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/</a></td>
</tr>
<tr>
<td>Gyle Square</td>
<td></td>
</tr>
<tr>
<td>1 South Gyle Crescent,</td>
<td></td>
</tr>
<tr>
<td>Edinburgh EH12 9EB</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Northern Ireland</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Information and Registration Unit</td>
<td>E-Mail: <a href="mailto:info.bso@hscni.net">info.bso@hscni.net</a></td>
</tr>
<tr>
<td>Family Practitioner Services</td>
<td>Website: <a href="http://www.hscbusiness.hscni.net/services/1806.htm">http://www.hscbusiness.hscni.net/services/1806.htm</a></td>
</tr>
<tr>
<td>Business Services Organisation</td>
<td></td>
</tr>
<tr>
<td>2 Franklin Street</td>
<td></td>
</tr>
<tr>
<td>Belfast BT2 8DQ</td>
<td></td>
</tr>
</tbody>
</table>
Appendix A: Selection of medicines and reason for decision

The table below shows the medicines that were considered for inclusion in this report by MEG. The principal reason is given for those medicines which are excluded. This appendix does not include those medicines excluded by the inclusion and exclusion criteria applied at the initial stage of the medicine selection process.

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Therapy area</th>
<th>Rationale for decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone in combination with prednisolone</td>
<td>Cancer: Prostate</td>
<td>Limited usage data available as there is significant supply via the homecare and outsourcing routes.</td>
</tr>
<tr>
<td>or prednisone (2nd line)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Coronary Syndromes - abciximab, eptifibatide, tirofiban</td>
<td>Acute Coronary Syndromes</td>
<td>Included: variation approach</td>
</tr>
<tr>
<td>Acute Coronary Syndromes - ticagrelor, prasugrel, clopidogrel</td>
<td>Acute Coronary Syndromes</td>
<td>Included: variation approach</td>
</tr>
<tr>
<td>Alitretinoin</td>
<td>Chronic hand eczema</td>
<td>Included: variation approach</td>
</tr>
<tr>
<td>Alteplase</td>
<td>Ischaemic stroke (acute)</td>
<td>Considered by MEG but excluded as too recently appraised.</td>
</tr>
<tr>
<td>Alzheimer’s disease - donepezil, galantamine,</td>
<td>Alzheimer’s disease</td>
<td>Included: estimate approach</td>
</tr>
<tr>
<td>rivastigmine, memantine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention deficit hyperactivity disorder (ADHD)</td>
<td>Attention deficit hyperactivity disorder (ADHD)</td>
<td>Included: variation approach</td>
</tr>
<tr>
<td>in children and adolescents - methylphenidate, atomoxetine and dexamfetamine</td>
<td>in children and adolescents</td>
<td></td>
</tr>
<tr>
<td>Azacitidine</td>
<td>Cancer of the blood</td>
<td>There are other options for treatment and a very small patient population.</td>
</tr>
<tr>
<td>Bendamustine (1st line)</td>
<td>Cancer of the blood</td>
<td>There are other options for treatment and a very small patient population.</td>
</tr>
<tr>
<td>Biologic drugs for Rheumatoid Arthritis:</td>
<td>Cancer of the blood</td>
<td></td>
</tr>
<tr>
<td>Infliximab, rituximab, etanercept, adalimumab,</td>
<td>Used for a range of autoimmune conditions</td>
<td>This group of medicines were presented as a special section of the previous report to</td>
</tr>
<tr>
<td>abatacept, certolizumab, tocolizumab and</td>
<td>including rheumatoid arthritis</td>
<td>explain the complexity associated with establishing an eligible population for some</td>
</tr>
<tr>
<td>golimumab</td>
<td></td>
<td>medicines where there are multiple indications and multiple appraised options for</td>
</tr>
<tr>
<td>Botulinum toxin type A</td>
<td>Migraine</td>
<td>treatment.. These issues remain and as a group they have been excluded from this report.</td>
</tr>
<tr>
<td>Breast cancer (early) - hormonal treatments:</td>
<td>Breast cancer (early)</td>
<td>This medicine has multiple indications and it is not possible to establish proportional</td>
</tr>
<tr>
<td>anastrozole, exemestane and letrozole</td>
<td>hormonal treatments:</td>
<td>usage.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td>Therapy area</td>
<td>Rationale for decision</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Cancer: Breast cancer</td>
<td>Capecitabine was included in section two of the previous report. This medicine has two indications, only one of which has been appraised and it is not possible to establish proportional use. In addition, capecitabine is recommended as a treatment option where other medicines are available and it is not possible to establish proportional use. There is no further information since last year to inform the estimate and so this medicine has been excluded from this report.</td>
</tr>
<tr>
<td>Carmustine implants</td>
<td>Cancer: Glioma</td>
<td>Included: estimate approach</td>
</tr>
<tr>
<td>Dexamethasone intravitreal implant</td>
<td>Macular oedema</td>
<td>This medicine is recommended as a treatment option where other options are available.</td>
</tr>
<tr>
<td>Diabetes (type 2) - exenatide and liraglutide</td>
<td>Diabetes (type 2)</td>
<td>Included: estimate approach</td>
</tr>
<tr>
<td>Diabetes - insulin glargine and insulin detemir</td>
<td>Diabetes</td>
<td>Included: estimate approach</td>
</tr>
<tr>
<td>Dronedarone (2nd line)</td>
<td>Non-permanent atrial fibrillation</td>
<td>A change in licensed indication means it is not possible to establish proportional usage to develop an estimate of eligible patients.</td>
</tr>
<tr>
<td>Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia</td>
<td>Primary (heterozygous-familial and non-familial) hypercholesterolaemia</td>
<td>Included: variation approach. The manufacturer would have preferred this medicine to be included in the estimate section, however, it was not possible to develop a suitable estimate.</td>
</tr>
<tr>
<td>Febuxostat</td>
<td>Chronic hyperuricaemia</td>
<td>Included: variation approach</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Multiple sclerosis</td>
<td>Limited usage data available as this medicine is supplied almost routinely via the homecare route.</td>
</tr>
<tr>
<td>Hepatitis C - peginterferon alfa-2a, peginterferon alfa-2b and ribavirin, boceprevir, telaprevir</td>
<td>Hepatitis C</td>
<td>Included: see estimate approach. Boceprevir, telaprevir were considered by MEG but excluded as too recently appraised.</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Cancer of the blood</td>
<td>Multiple alternative treatments are available. Limited usage data available as significant supply via the homecare route.</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Cancer: Skin</td>
<td>Considered by MEG but excluded as too recently appraised.</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Chronic heart failure</td>
<td>Considered by MEG but excluded as too recently appraised.</td>
</tr>
<tr>
<td>Lung cancer (non-small cell, EGFR-TK mutation positive) - erlotinib (1st line)</td>
<td>Lung cancer (non-small cell, EGFR-TK mutation positive) (1st line)</td>
<td>Included: variation approach</td>
</tr>
<tr>
<td>Lung cancer (non-small cell, first line) – gefitinib</td>
<td>Lung cancer (non-small cell, first line)</td>
<td>Included: variation approach</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Medicine</th>
<th>Therapy area</th>
<th>Rationale for decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mifamurtide</td>
<td>Cancer: Bone</td>
<td>There is a small eligible population and this medicine is primarily used to treat children, adolescents and young adults.</td>
</tr>
<tr>
<td>Multiple Myeloma - bortezomib, lenalidomide, thalidomide</td>
<td>Multiple Myeloma</td>
<td>Included: variation approach</td>
</tr>
<tr>
<td>Myocardial infarction (persistent ST-segment elevation) – bivalirudin</td>
<td>Myocardial infarction (persistent ST-segment elevation)</td>
<td>Included: variation approach</td>
</tr>
<tr>
<td>Naftidrofyryl oxalate</td>
<td>Peripheral arterial disease</td>
<td>This medicine has multiple indications and it is not possible to establish proportional usage</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Drug and alcohol misuse</td>
<td>This medicine was presented in section one of the previous year's report. There are problems establishing a value for the proportion of quitters using this medicine rather than alternatives. In addition, naltrexone is also used in the treatment of alcohol misuse and it is not possible to establish proportional usage.</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Cancer of the blood</td>
<td>Multiple alternative treatments are available and patient numbers are low so there is a risk of disclosure.</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Asthma</td>
<td>This medicine was presented in section two of the previous report. There is significant supply via the home care route. The company regarded their data as commercially sensitive information. Since it was not possible to obtain suitable usage data, this medicine was excluded from the report.</td>
</tr>
<tr>
<td>Prevention of osteoporotic fragility fractures - alendronate, etidronate, risedronate, raloxifene, strontium ranelate, and teriparatide</td>
<td>Prevention of osteoporotic fragility fractures</td>
<td>Included: variation approach</td>
</tr>
<tr>
<td>Prevention of osteoporotic fractures - denosumab</td>
<td>Prevention of osteoporotic fractures</td>
<td>Included: variation approach</td>
</tr>
<tr>
<td>Prevention of venous thromboembolism after hip or knee replacement surgery - dabigatran etexilate, apixaban and rivaroxaban</td>
<td>Prevention of venous thromboembolism after hip or knee replacement surgery</td>
<td>Included: variation approach</td>
</tr>
<tr>
<td>Prevention of stroke and systemic embolism in atrial fibrillation – dabigatran etexilate and rivaroxaban</td>
<td>Prevention of stroke and systemic embolism in atrial fibrillation</td>
<td>Included: variation approach</td>
</tr>
<tr>
<td>Prucalopride</td>
<td>Chronic constipation in women</td>
<td>Included: variation approach The manufacturer would have preferred this medicine to be included in the estimate section, however, it was not possible to develop a suitable estimate.</td>
</tr>
<tr>
<td>Medicine</td>
<td>Therapy area</td>
<td>Rationale for decision</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pharmalgen</td>
<td>Treatment of bee and wasp venom allergy</td>
<td>There is a small patient population and the ability to estimate the eligible population.</td>
</tr>
<tr>
<td>Pioglitazone in combination with a sulphonylurea</td>
<td>Type 2 diabetes</td>
<td>This medicine has been removed from the report due to MHRA safety announcements relating to cardiovascular safety and a small increased risk of bladder cancer. These warnings change the estimate of eligible patients.</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>Wet age-related macular degeneration</td>
<td>Included: estimate approach</td>
</tr>
<tr>
<td>Renal cell carcinoma - sunitinib and pazopanib</td>
<td>Renal cell carcinoma</td>
<td>Included: estimate approach</td>
</tr>
<tr>
<td>Retigabine (adjuvant)</td>
<td>Epilepsy</td>
<td>This medicine is recommended as a treatment option where other options are available.</td>
</tr>
<tr>
<td>Riluzole</td>
<td>Amyotrophic lateral sclerosis</td>
<td>Included: estimate approach</td>
</tr>
<tr>
<td>Rituximab (1st line maintenance treatment)</td>
<td>Cancer: Lymphatic system</td>
<td>This medicine has multiple indications and it is not possible to establish proportional usage.</td>
</tr>
<tr>
<td>Romiplostim</td>
<td>Autoimmune disease: platelets</td>
<td>There is a very small patient population of less than five hundred, so there is a risk of disclosure.</td>
</tr>
<tr>
<td>Schizophrenia - aripiprazole</td>
<td>Schizophrenia</td>
<td>A recommended option for 15 to 17 year olds with schizophrenia who are unresponsive or unsuitable for risperidone. It is not possible to establish use in specific age groups.</td>
</tr>
<tr>
<td>Statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin)</td>
<td>Lipid-regulation</td>
<td>This group of medicines were presented in section one of the previous report. Their position in therapy is well established and their use is reported elsewhere and so they have been excluded from this year's report. However, they have been included in the denominator for the ezetimibe variation charts.</td>
</tr>
<tr>
<td>Short-term management of insomnia - zaleplon, zolpidem and zopiclone</td>
<td>Short-term management of insomnia</td>
<td>Included: variation approach</td>
</tr>
<tr>
<td>Smoking cessation - varenicline</td>
<td>Smoking cessation</td>
<td>Included: variation approach</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>Cancer: Glioma</td>
<td>Included: estimate approach</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Cancer: Breast cancer, gastric cancer</td>
<td>Included: estimate approach</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Cancer: Skin</td>
<td>Considered by MEG but excluded as a too recently appraised medicine.</td>
</tr>
</tbody>
</table>