

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## GUIDANCE EXECUTIVE (GE)

### Review of TA265; Denosumab for treating bone metastases from solid tumours

This guidance was issued in October 2012

The review date for this guidance in July 2013

#### 1. Recommendation

A part review of TA265 should be planned into the appraisal work programme for recommendation 1.1. Recommendation 1.2 should be transferred to the 'static guidance list'. That we consult on this proposal.

#### 2. Original remit(s)

To appraise the clinical and cost effectiveness of denosumab within its licensed indication for the treatment of bone metastases from solid tumours and multiple myeloma.

#### 3. Current guidance

- 1.1. Denosumab is recommended as an option for preventing skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from breast cancer and from solid tumours other than prostate if:
  - bisphosphonates would otherwise be prescribed **and**
  - the manufacturer provides denosumab with the discount agreed in the patient access scheme.
- 1.2. Denosumab is not recommended for preventing skeletal-related events in adults with bone metastases from prostate cancer.
- 1.3. Adults with bone metastases from solid tumours currently receiving denosumab for the prevention of skeletal-related events that is not recommended according to 1.1 and 1.2 should be able to continue treatment until they and their clinician consider it appropriate to stop.

#### **4. Rationale<sup>1</sup>**

TA265 outlines that the cost-effectiveness of denosumab is sensitive to the price of the comparator zoledronic acid. Many generic manufacturers have received marketing authorisation for zoledronic acid recently and significant reductions in price are expected with the market launch of generic versions. With zoledronic acid available at lower costs, denosumab may not be a cost-effective option for preventing skeletal related event in people with bone metastases from breast cancer and from solid tumours other than prostate.

In the prostate cancer population, denosumab is not recommended in TA265. There is no information available which could potentially lead to change in this recommendation.

#### **5. Implications for other guidance producing programmes**

There is no proposed or ongoing guidance development that overlaps with this review proposal.

#### **6. New evidence**

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from March 2011 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. No additional, ongoing or unpublished phase III/IV trials were found. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below.

#### **7. Summary of evidence and implications for review**

##### **Marketing authorisations and costs**

Since TA265 was published, the marketing authorisation and price of denosumab (XGEVA, Amgen) remain unchanged and the manufacturer has shown willingness to continue with the patient access scheme in its current form, without any changes.

In TA 265 bisphosphonates were considered comparators for denosumab for people with bone metastases from breast cancer and the people with solid tumours other than breast and prostate, while in people with bone metastases from prostate cancer, best supportive care was considered the appropriate comparator.

For patients with bone metastases from breast cancer and solid tumours other than breast and prostate cancer, zoledronic acid (which is the most widely used bisphosphonate in these indications) was considered as the main comparator. It has recently come off patent and many generic manufacturers have received marketing authorisation for zoledronic acid since then. The price of generic zoledronic acid is not yet available in public domain although Novartis, the patent holder of zoledronic acid at the time of appraisal, had anticipated at least 50% drop in the price after it

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<sup>1</sup> A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

would become generic. The Appraisal Committee had noted that the ICERs, which underpinned the decision to recommend denosumab were highly sensitive to the price of the comparator and recommended an early consideration for review after generic zoledronic acid would be available.

For the prostate cancer population, best supportive care was considered the comparator, because NICE clinical guideline 58 did not recommend bisphosphonates for the prevention of skeletal related events in people with bone metastases from prostate cancer. NICE CG 58 is currently being updated but the use of bisphosphonates is not being considered in the review, hence the negative recommendation on the use of bisphosphonates for preventing skeletal related events is not expected to change, and best supportive care would remain the appropriate comparator for denosumab for this population.

## **Clinical Evidence**

The literature searches did not identify any new published clinical evidence which is likely to lead to a change in the conclusions made by the Committee about the clinical effectiveness of denosumab.

A recent systematic review looking into the efficacy and safety of denosumab in reducing skeletal-related events in patients with bone metastases across all solid tumours and multiple myeloma, included 3 phase II studies in addition to 3 phase III studies included in the clinical evidence considered by the Committee (Peddi et al., 2013). Similarly a Cochrane review on bisphosphonates and other bone agents for breast cancer (Wong et al., 2012) identified 3 trials, comparing denosumab with bisphosphonates (1 phase III and 2 phase II). These phase II trials had been identified by the Assessment Group but were excluded from the evidence synthesis because of various methodological reasons, however, results of both meta-analyses were consistent with conclusion made by the Committee, that denosumab was more effective than zoledronic acid in reducing the incidence of skeletal related events and in delaying the time to skeletal related event while no differences were found between in reducing overall survival, or in the frequency of overall adverse events.

Two abstracts (Richardson et al., 2012 and Body et al., 2012) analysed health resource utilisation associated with skeletal-related events in the phase III RCTs and concluded that skeletal-related events are associated with increased health resource utilization. It should be noted that the economic analyses underpinning the previous recommendations assumed cost associated with skeletal related events.

In two separate open-label extension studies, one in patients with bone metastases from breast cancer (De Boer, 2012) and another in prostate cancer (Kueppers et al., 2012) who completed the phase III randomized trials, patients were offered to continue receiving denosumab or switch to denosumab from zoledronic acid. Patients were followed-up for further 2 years and adverse events in people who were initially randomised to denosumab and continued to receive it were compared with people who switched to denosumab from zoledronic acid at unblinding. Based on comparable rate of adverse events in these two groups the authors concluded that these studies confirmed the long-term safety profile of denosumab. Another post-hoc safety analysis (Saad et al. 2012) reported incidence, risk factors, and outcomes of osteonecrosis of the jaw, from integrated data of 3 phase III trials.

In a commentary on the development of denosumab, Goessl et al. (2012) included published results of 3 phase III trials. Some other studies reported further analyses from the phase III trials, for example in the breast cancer population, Martin et al. (2012) reported the proportion of patients with one or multiple on-study skeletal related event, time to first radiation to bone, time to first skeletal related event or hypercalcemia of malignancy, and change in health related quality of life and Cleeland et al. (2013) reported data on pain outcomes. Similarly from phase III trial, in patients with bone metastases from prostate cancer, Dranitsaris and Kaura (2011) reported numbers needed to treat (NNT) to avoid a single skeletal related event as well as to avoid individual components of skeletal related events (pathological fracture, radiation to bone, spinal cord compression and surgery to bone) and Patrick et al. (2012) reported data on pain outcome and in the people with bone metastases from solid tumours other than breast and prostate Fallowfield et al. (2011) reported data on pain outcome. Most of the data reported in these studies, somehow, had already been considered by the Committee at the time of appraisal.

Many other published studies included data from people with multiple myeloma which is not covered in the marketing authorisation and are not detailed here (Lipton et al., 2011, von Moos et al., 2010a, von Moos et al., 2010b, Richardson et al., 2011, Vadhan-Raj et al. 2012).

In summary, there is no new published clinical evidence besides data on long-term safety of denosumab. There is no relevant on-going clinical trial, and it may not be necessary to review the clinical-effectiveness of denosumab now. However, given the expected decrease in the price of the comparator, there is a strong rationale for reviewing the cost-effectiveness of denosumab in adults with bone metastases from breast cancer and from solid tumours other than prostate.

## **8. Implementation**

A submission from Implementation is included in Appendix 3. The submission includes data on net ingredient cost (NIC) and volume of denosumab prescribed and dispensed in hospitals in England for its multiple indications. The Hospital Pharmacy Audit Index (HPAI) data show a steady increase in the use of denosumab between April 2009 and January 2012. The electronic prescribing analysis and cost tool (ePACT) data also show a slight decrease in denosumab use between October 2012 and December 2012 corresponding to the publication of TA265, probably reflecting the impact of not recommending denosumab in patients with bone metastases from prostate cancer. It should be noted that these data also include use of denosumab in other indications for example osteoporosis and therefore it is not possible to draw any definitive conclusions about the use in the population appraised in TA265.

## **9. Equality issues**

It was highlighted during the appraisal process that the fact that denosumab is recommended for the treatment of breast cancer but not for the treatment of prostate cancer could be interpreted as indirect sex discrimination. This is because the vast majority of people with breast cancer are women, and prostate cancer can only occur in biological men (cisgender men and transgender women).

**GE paper sign off:** Elisabeth George, 21 06 13

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## Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – ‘Yes/No’
<b>A review of the guidance should be planned into the appraisal work programme.</b>	A review of the appraisal will be planned into the NICE’s work programme.	<b>Yes (for recommendation 1.1)</b>
The decision to review the guidance should be deferred.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	<p>The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review.</p> <p>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.</p>	No
The guidance should be updated in an on-going clinical guideline.	<p>Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.</p> <p>Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).</p>	No

Options	Consequence	Selected – ‘Yes/No’
<b>The guidance should be transferred to the ‘static guidance list’.</b>	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	<b>Yes (for recommendation 1.2)</b>

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

- i. The technology falls within the scope of a clinical guideline (or public health guidance)
- ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement
- iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment
- iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;
  - Spending on a treatment for the indication which was the subject of the appraisal continues to rise
  - There is evidence of unjustified variation across the country in access to a treatment
  - There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
  - The treatment is excluded from the Payment by Results tariff
- v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

## Appendix 2 – supporting information

### Relevant Institute work

#### *Published*

Lung cancer: the diagnosis and treatment of lung cancer. Clinical Guideline CG121. Issued: April 2011. Review date: April 2014.

Lung cancer. Quality Standard QS18. Issued: May 2012. Review date: May 2017.

Advanced breast cancer: diagnosis and treatment. Clinical Guideline CG81. Issued: February 2009. A decision not to review this guidance was taken in 2012. This guideline will be considered for review again in 2013 to enable recent Technology Appraisals to be taken into consideration.

Breast cancer. Quality Standard QS12. Issued: September 2011. Review date: September 2016.

Metastatic spinal cord compression: diagnosis and management of adults at risk of and with metastatic spinal cord compression. Clinical Guideline CG75. Issued: November 2008. This guidance was considered for review in 2012 and it was decided not to update at that time.

Prostate cancer: diagnosis and treatment. Clinical Guideline CG58. Issued: February 2008. An update of this guideline is currently in progress.

Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults. Clinical Guideline 140. Issued: May 2012. Review date: May 2015.

#### *In progress*

Radium-223 dichloride for treating metastatic hormone relapsed prostate cancer with bone metastases [ID576]. Technology Appraisal. Expected issue date: January 2014.

Prostate cancer: diagnosis and management (review of CG58). Clinical Guideline. Expected issue date: January 2014.

#### *Suspended/terminated*

Bone metastases (hormone refractory prostate cancer) - denosumab [ID405]. The manufacturer of denosumab has informed NICE that they will not provide a submission for this appraisal. NICE has therefore suspended this appraisal, which would have covered a possible license extension to include use in people with non-metastatic hormone relapsed prostate cancer who are at high risk of developing bone metastases.



## Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.	<p>No change.</p> <p>Denosumab is currently in a phase III trial for the prevention of skeletal-related events in patients with bony lesions from multiple myeloma. The estimated study completion date is July 2016.</p> <p>A proposed indication for use in people with non-metastatic hormone relapsed prostate cancer who are at high risk of developing bone metastases is covered elsewhere on the NICE work programme.</p>

## Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date, )
Radium-223 chloride (Bayer)	Phase II for treatment of bone metastases in people with breast cancer (launch plans unknown); pre-registration filings made for treatment of bone metastases from hormone relapsed prostate cancer – UK launch anticipated [REDACTED].

## References

Peddi P, Lopez-Olivo MA, Pratt GF et al. (2013) Denosumab in patients with cancer and skeletal metastases: A systematic review and meta-analysis. *Cancer Treatment Reviews* 39 (1): 97-104.

Wong MHF, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. *Cochrane Database of Systematic Reviews* 2012, Issue 2. Art. No.: CD003474. DOI: 10.1002/14651858.CD003474.pub3.

Richardson G, Body J-J, von MR et al. (2012) Health resource utilisation (HRU) and patient burden associated with skeletal-related events (SRES) in a randomised controlled trial setting. *Asia-Pacific Journal of Clinical Oncology* 8: 354.

Body J-J, Moos RV, Saad F et al. (2012) Health resource utilization and patient burden associated with SREs in a randomized controlled trial setting. *Journal of Clinical Oncology* 30 (15 SUPPL. 1).

De Boer RH, Stopeck AT, Lipton A et al. (2012) Plenary session-best of the best research in 2012 abstracts denosumab in patients with breast cancer and bone metastases previously treated with zoledronic acid or denosumab: A pre-specified

two year open-label extension treatment phase of a pivotal phase iii study. *Asia-Pacific Journal of Clinical Oncology* 8: 44.

Kueppers F, Fizazi K, Brown J et al. (2013) 2-year open-label extension phase results from the pivotal phase 3 study of denosumab in patients with metastatic castration-resistant prostate cancer (CRPC) previously treated with denosumab or zoledronic acid. *BJU International* 111: 91-92.

Saad F, Brown JE, Van PC et al. (2012) Incidence, risk factors, and outcomes of osteonecrosis of the jaw: Integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. *Annals of Oncology* 23 (5): 1341-1347.

Goessl C, Katz L, Dougall WC et al. (2012) The development of denosumab for the treatment of diseases of bone loss and cancer-induced bone destruction. *Ann. New York Acad. Sci.* 1263 (1): 29-40.

Martin M, Bell R, Bourgeois H et al. (2012) Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab versus zoledronic acid. *Clinical Cancer Research* 18 (17): 4841-4849.

Cleeland CS, Body JJ, Stopeck A et al. (2013) Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. *Cancer* 119 (4): 832-838.

Dranitsaris G, Kaura S (2011) The number needed to treat (NNT) as a measure of incremental drug benefit: Denosumab vs. Zoledronic acid for the prevention of skeletal related events (sres) in castration-Resistant prostate cancer (CRPC). *European Journal of Cancer* 47: S259.

Patrick D, Cleeland C, Fallowfield L et al. (2012) Pain interference with daily functioning in patients with castrate-resistant prostate cancer: A comparison of denosumab and zoledronic acid. *Journal of Urology* 187 (4 SUPPL. 1): e384.

Fallowfield L, von MR, Patrick D et al. (2011) Pain outcomes in a randomized phase 3 clinical trial of denosumab vs zoledronic acid (ZA) in patients with solid tumours and bone metastases. *European Journal of Cancer* 47: S485.

Lipton A, Fizazi K, Stopeck AT et al. (2011) Prevention of skeletal-related events with denosumab or zoledronic acid - Combined analysis from 3 registrational trials. *European Journal of Cancer* 47: S240.

von MR, Vadhan S, Henry D et al. (2010) Exploratory analyses from a randomised phase 3 trial treating bone metastases (BM) from advanced solid tumours (not including breast or prostate) or multiple myeloma (MM) with denosumab or zoledronic acid (ZA). *Onkologie* 33 (6): 62

von MR, Patrick D, Fallowfield L et al. (2010) Pain management in patients (pts) with advanced cancer (excluding breast and prostate) or multiple myeloma (MM): Results from a randomised phase 3 clinical trial of denosumab versus zoledronic acid (ZA). *Onkologie* 33 (6): 76-77.

Richardson G, Ciuleanu TE, Costa L et al. (2011) A number needed to treat analysis of denosumab versus zoledronic acid in patients with bone metastases/lesions secondary to solid tumours (other than breast and prostate) or multiple myeloma. *Asia-Pacific Journal of Clinical Oncology* 7: 144.

Vadhan-Raj S, von MR, Fallowfield LJ et al. (Dec. 2012) Clinical benefit in patients with metastatic bone disease: results of a phase 3 study of denosumab versus zoledronic acid. *Annals of Oncology* 23 (12): 3045-3051.

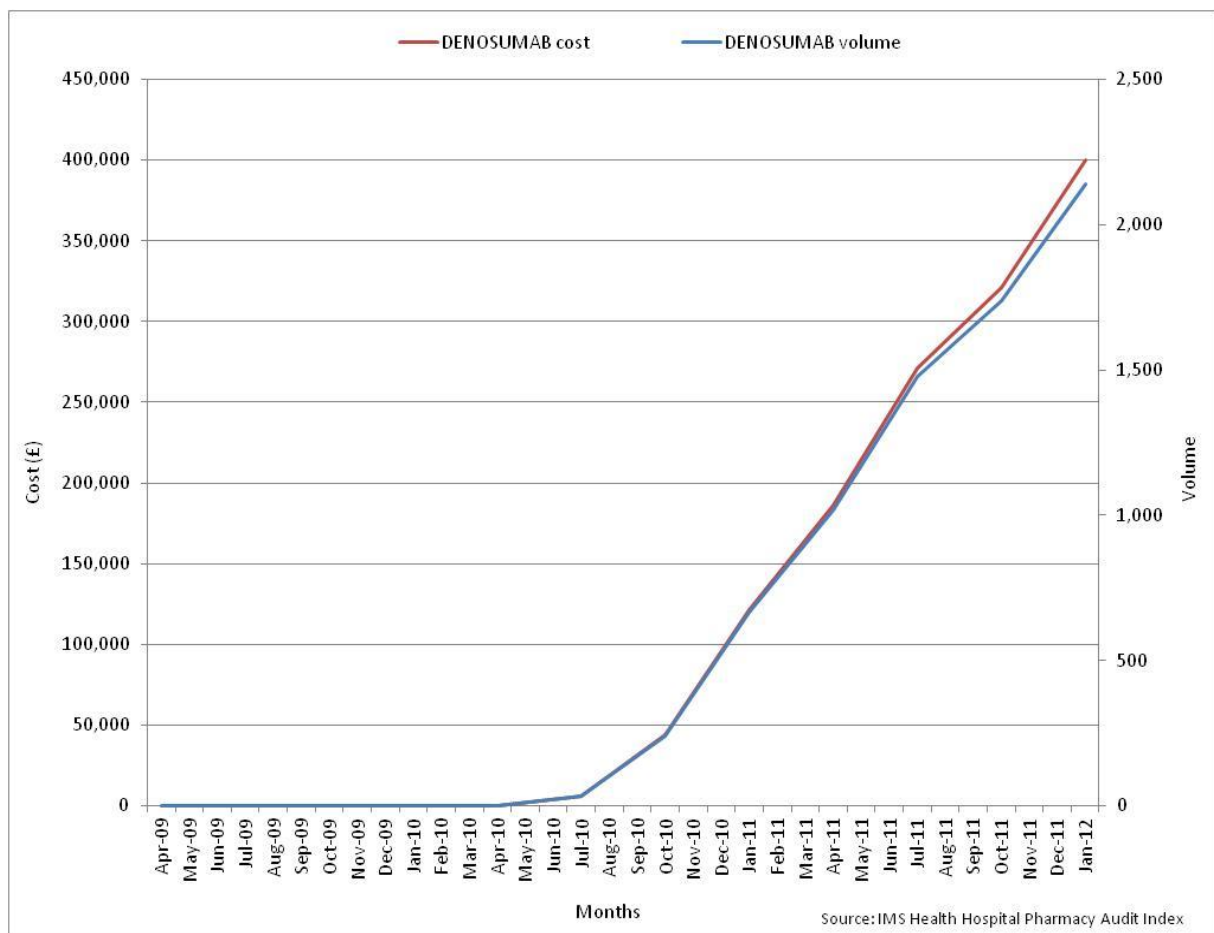
## Appendix 3 – Implementation submission

### Routine healthcare activity data

#### 1.1 Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index (HPAI) data on the net ingredient cost (NIC) and volume of Denosumab prescribed and dispensed in hospitals in England between April 2009 and January 2012. These data need to be treated with caution as Denosumab has multiple indications. These data are not linked to a diagnosis of bone metastases from solid tumours.

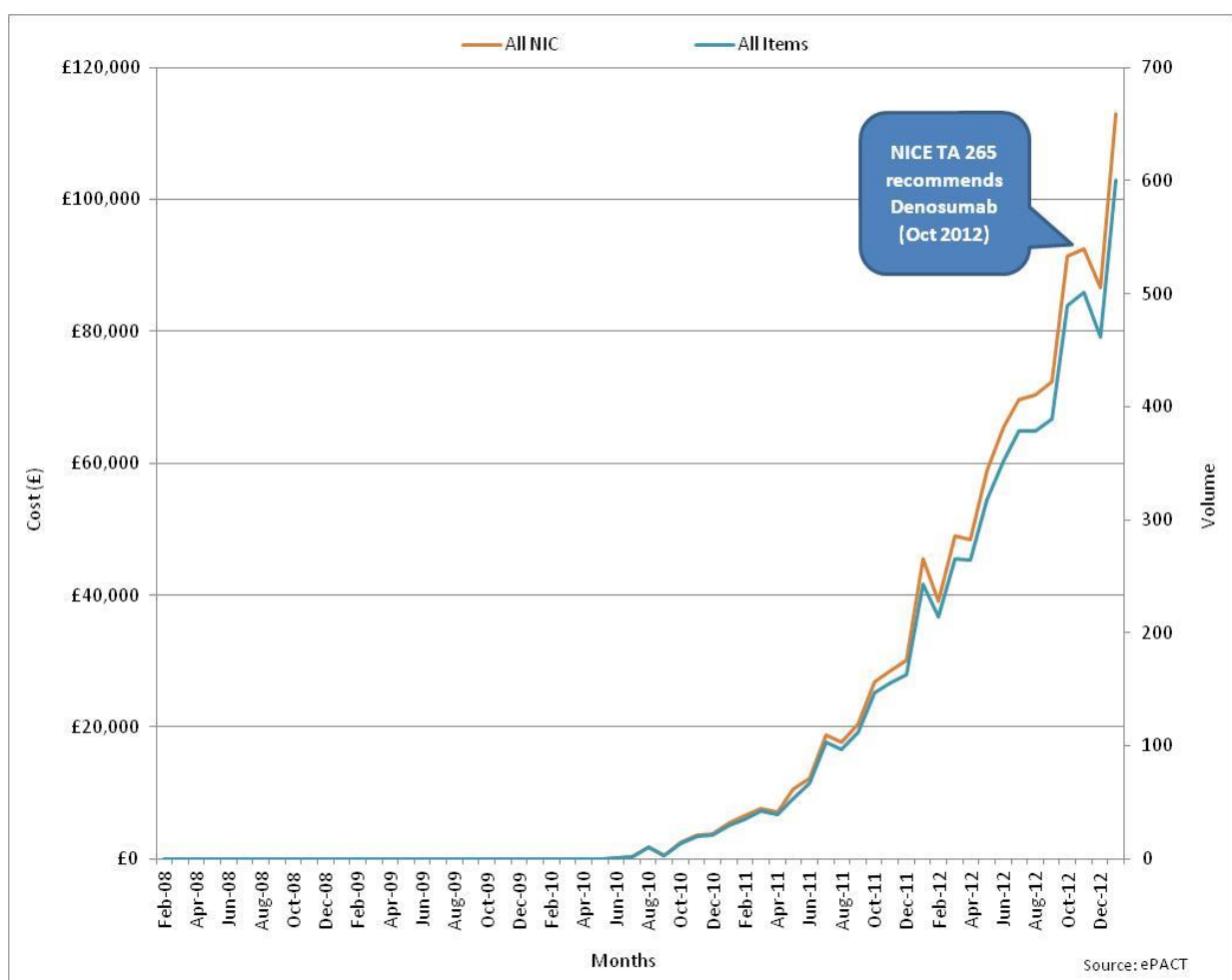
**Figure 1 Cost and volume of Denosumab prescribed in hospitals in England**



## 1.2 ePACT data

This section presents electronic prescribing analysis and cost tool (ePACT) data on the net ingredient cost (NIC) and volume of denosumab prescribed in primary care and in hospitals and dispensed in the community in England between February 2008 and January 2013. These data need to be treated with caution as denosumab has multiple indications. These data are not linked to a diagnosis of bone metastases from solid tumours.

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



## 1 Implementation studies from published literature

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

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

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

## **2 Qualitative input from the field team**

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

Nothing to add at this time.

## **Addendum: Healthcare activity data definitions**

### *Prescribing analysis and cost tool system*

This information comes from the electronic prescribing analysis and cost tool (ePACT) system, which covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Services Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions dispensed in hospitals or mental health units, and private prescriptions, are not included in PACT data.

### ***Measures of prescribing***

**Prescription Items:** Prescriptions are written on a prescription form. Each single item written on the form is counted as a prescription item. The number of items is a measure of how many times the drug has been prescribed.

**Cost:** The net ingredient cost (NIC) is the basic price of a drug listed in the drug tariff, or if not in the drug tariff, the manufacturer's list price.

### ***Data limitations (national prescriptions)***

PACT data do not link to demographic data or information on patient diagnosis. Therefore the data cannot be used to provide prescribing information by age and sex or prescribing for specific conditions where the same drug is licensed for more than one indication

### *IMS HEALTH Hospital Pharmacy Audit Index (IMS HPAI)*

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies: to wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

### ***Measures of prescribing***

**Volume:** The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

***Data limitations***

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.