NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA239; Fulvestrant for the treatment of locally advanced or metastatic breast cancer

This guidance was issued in December, 2011

The review date for this guidance is August, 2014

1. Recommendation

The guidance 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 high dose (500mg) fulvestrant within its licensed indication for the treatment of locally advanced or metastatic breast cancer.

3. Current guidance

1.1. Fulvestrant is not recommended, within its licensed indication, as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer in postmenopausal women whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy.

1.2. Post-menopausal women currently receiving fulvestrant within its licensed indication as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy, should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

4. Rationale[1]

No new relevant clinical evidence has emerged that is expected to affect the recommendations in TA239. Fulvestrant is not expected to receive an extension to its marketing authorisation. The NHS list price of fulvestrant has not changed since the original appraisal. TA239 did not include any specific recommendations for

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

further research. In view of the above information, an update of TA239 is not considered necessary.

5. Implications for other guidance producing programmes

TA239 overlaps with both CG80 (Breast cancer (early & locally advanced): diagnosis and treatment) and CG81 (Advanced breast cancer: diagnosis and treatment). An update of CG81 (Advanced breast cancer – update) published on 1st July 2014. The recommendations within TA239 were not included in the update of the guideline.

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 January, 2010 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

The marketing authorisation for fulvestrant places fulvestrant as an alternative to aromatase inhibitors after anti-oestrogen treatment (that is, second line), and third-line or fourth-line use was not considered within the remit of the appraisal.

In TA239, the key trial for fulvestrant compared the 500 mg dose with the 250 mg dose of fulvestrant. Only interim data on overall survival were available.

Since TA239 was issued, mature survival data have been published (Di Leo et al. 2013). Although stronger, the new evidence showed very similar hazard ratios, and is unlikely to change the recommendations in TA239 given that the Committee had concluded that fulvestrant 500 mg offered some clinical benefit compared with fulvestrant 250 mg.

The decisions in TA239 were based on a network meta-analysis comparing overall survival and time to progression for fulvestrant 500 mg with anastrozole or letrozole, but the Committee considered that this analysis had limitations. Although this review identified several studies on fluvestrant, none compared fluvestrant with anastrozole or letrozole, directly or indirectly, for the relevant population.

The Committee did not make specific recommendations for further research.

Fulvestrant is not expected to receive an extension to its marketing authorisation.

The NHS list price of fulvestrant has not changed since the original appraisal.

In view of the above information, an update of TA239 is not considered necessary.

8. Implementation

A submission from Implementation is included in Appendix 3.

The cost and volume of fulvestrant prescribed in hospitals in England has been declining since TA239 was published. This is expected given that fulvestrant was not recommended in the guidance. Fulvestrant is not funded through Cancer Drugs Fund.

9. Equality issues

The Committee considered a potential equality issue highlighted during consultation about the use of fulvestrant for patients unable to swallow oral aromatase inhibitor medication. The Committee was aware that women who are unable to swallow (for example, following a stroke) would be fed using an enteral tube, and that oral medication can also be given by this route. In addition, given that the recommendation did not differentiate between any groups of people, the Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups.

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Appendix 1 – explanation of options

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

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the [specify STA or MTA] process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	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. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

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

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

CG80 Breast cancer (early & locally advanced): diagnosis and treatment Issued: February 2009. Reviewed June 2012 - decided not to update the guideline at this stage

Clinical guidelines CG81 Advanced breast cancer: diagnosis and treatment Issued: February 2009. Reviewed April 2012 - this guideline is currently being updated.

Clinical guidelines CG164 Familial breast cancer: classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer.Issued: June 2013. No review date

Technology appraisals TA112 Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer Issued: November 2006. Reviewed: October 2009 - transferred to static list

Technology appraisals TA116 Gemcitabine for the treatment of metastatic breast cancer. Issued: January 2007. Reviewed: May 2010 - transferred to static list

Technology appraisals TA214 Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer Issued: February 2011 Reviewed: September 2013 - transferred to static list

Technology appraisals TA250 Eribulin for the treatment of locally advanced or metastatic breast cancer Issued: April 2012 Review date: November 2014

Technology appraisals TA257 Breast cancer (metastatic hormone-receptor) - lapatinib and trastuzumab (with aromatase inhibitor) (TA257) Issued: June 2012 Review date: June 2015

Technology appraisals TA263 Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer Issued: August 2012 Review date: June 2015

Diagnostics guidance DG8 Intraoperative tests (RD‑100i OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer Issued: August 2013. Review date: August 2016

Diagnostics guidance DG10 Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat (DG10) Issued: September 2013 Review date: Septemnber 2016

In progress

Technology appraisals Intrabeam radiotherapy system for treating early breast cancer [ID618] Expected date of issue: November 2014

Referred - QSs and CGs

Quality Standard QS12 Breast cancer quality standard Issued: September 2011

Suspended/terminated

Technology appraisals Ixabepilone for locally advanced or metastatic breast cancer [ID377] Suspended - the manufacturer received a negative CHMP opinion for Ixabepilone for locally advanced or metastatic breast cancer (December 2008).

Technology appraisals Sunitinib in combination with capecitabine within its licensed indication for the treatment of advanced and/or metastatic breast cancer [ID319] Suspended - the manufacturer of sunitinib advised NICE that regulatory approval for this technology was not being sought at this time following the receipt of trial data (April 2010).

Technology appraisals Bevacizumab for the second line treatment of HER2 negative metastatic breast cancer [ID488]. Suspended - the manufacturer decided not to apply for a centralised marketing authorisation for this indication.

Technology appraisals Lapatinib in combination with paclitaxel for the first-line treatment of metastatic breast cancer which over-expresses ErbB2 (HER2) receptor [ID517]. Suspended - the manufacturer withdrew its application for a centralised marketing authorisation

Registered and unpublished trials

Trial name and registration number	**Details**
Palbociclib (PD-0332991) Combined With Fulvestrant In Hormone Receptor+ HER2-Negative Metastatic Breast Cancer After Endocrine Failure (PALOMA-3) (NCT01942135)	Estimated Enrolment: 417 Estimated Study Completion Date: January 2017 This study is currently recruiting participants
Fulvestrant With or Without Lapatinib in Treating Postmenopausal Women With Stage III or Stage IV Breast Cancer That is Hormone Receptor-Positive (NCT00390455)	Estimated Enrolment: 324 Estimated Primary Completion Date: July 2014 This study is ongoing, but not recruiting participants
Phase III Study of BKM120/Placebo With Fulvestrant in Postmenopausal Patients With Hormone Receptor Positive HER2-negative Locally Advanced or Metastatic Breast Cancer Refractory to Aromatase Inhibitor (BELLE-2) (NCT01610284)	Estimated Enrolment: 1060 Estimated Study Completion Date: March 2017 This study is currently recruiting participants

Trial name and registration number	Details
A Global Study to Compare the Effects of Fulvestrant and Arimidex in a Subset of Patients With Breast Cancer. (FALCON) (NCT01602380)	Estimated Enrolment: 605 Estimated Study Completion Date: September 2017 This study is currently recruiting participants
Fulvestrant With or Without Anastrozole or Exemestane Alone in Treating Postmenopausal Women With Locally Advanced or Metastatic Breast Cancer (NCT00253422)	Estimated Enrollment: 750 Estimated Primary Completion Date: May 2016 This study is ongoing, but not recruiting participants
A Phase III Study of BKM120 With Fulvestrant in Patients With HR+,HER2-, AI Treated, Locally Advanced or Metastatic Breast Cancer Who Progressed on or After mTORi (BELLE-3) (NCT01633060)	Estimated Enrollment: 420 Estimated Study Completion Date: March 2017 This study is currently recruiting participants
Fulvestrant and/or Anastrozole in Treating Postmenopausal Patients With Stage II-III Breast Cancer Undergoing Surgery (NCT01953588)	Estimated Enrollment: 2820 Estimated Primary Completion Date: April 2016 This study is currently recruiting participants
A Study of LY2835219 Combined With Fulvestrant in Women With Hormone Receptor Positive HER2 Negative Breast Cancer (MONARCH 2) (NCT02107703)	Estimated Enrollment: 550 Estimated Study Completion Date: February 2020 This study is not yet open for participant recruitment
S1222 Trial (Everolimus, Anastrozole and Fulvestrant) in Post-Menopausal Stage IV Breast Cancer (NCT02137837)	Estimated Enrollment: 825 Estimated Study Completion Date: May 2018 This study is not yet open for participant recruitment

Relevant services covered by NHS England specialised commissioning

Breast radiotherapy injury rehabilitation service (This service is for a discrete cohort of about 225 women who have severe, chronic and complex conditions arising from radiation-induced injuries. The women received a treatment regime for breast cancer in the 1970s and 1980s that is now known to be associated with a particular risk of damage to the nerves of the brachial plexus.)

Appendix 3 – Implementation submission

Review of NICE technology appraisal guidance No.239; Fulvestrant for the treatment of locally advanced or metastatic breast cancer

Contents

Please contact Liesl Millar regarding any queries Liesl.Millar@nice.org.uk

1. Routine healthcare activity data

1.1. ePACT data

This section presents electronic prescribing analysis and cost tool (ePACT) data on the net ingredient cost (NIC) and volume of fulvestrant prescribed and dispensed in hospitals in England between March 2009 and March 2014.

Figure 1 Cost and volume of fulvestrant prescribed and dispensed in hospitals in England between March 2009 and March 2014.

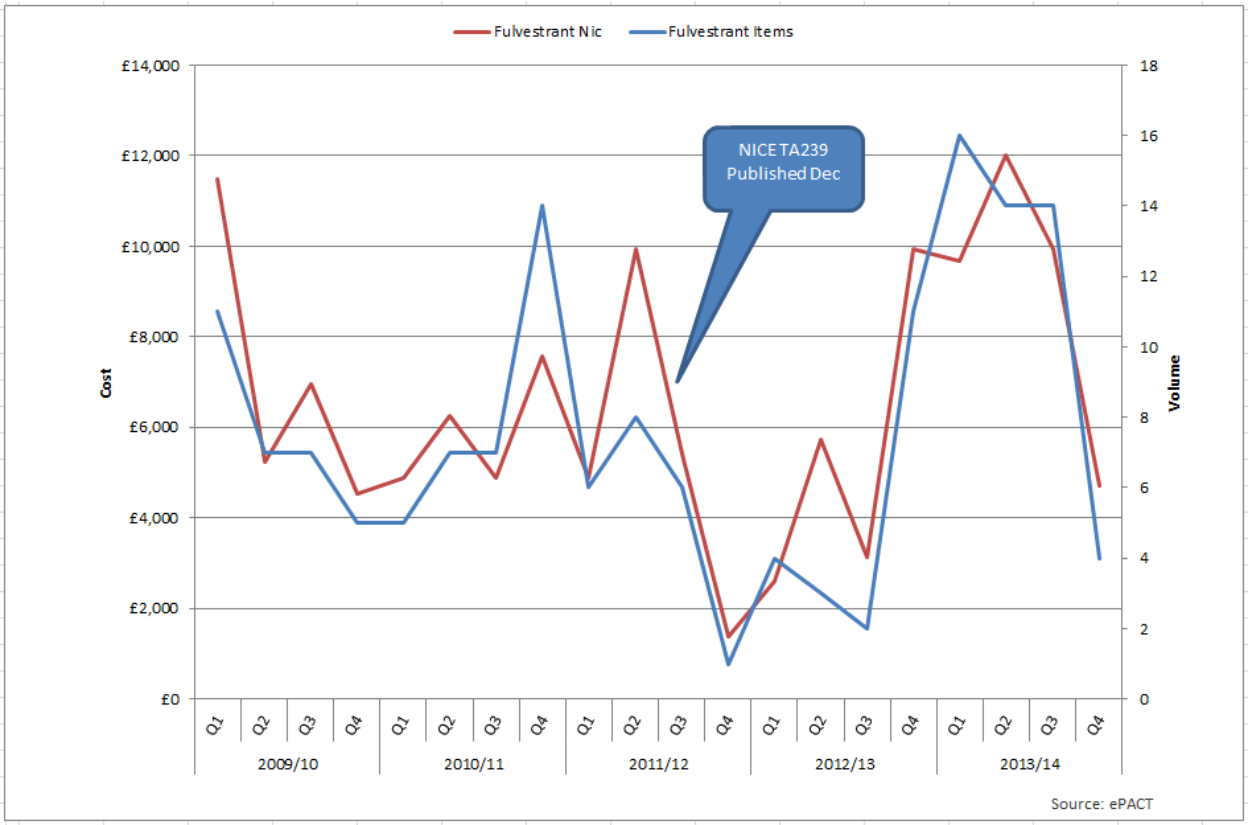
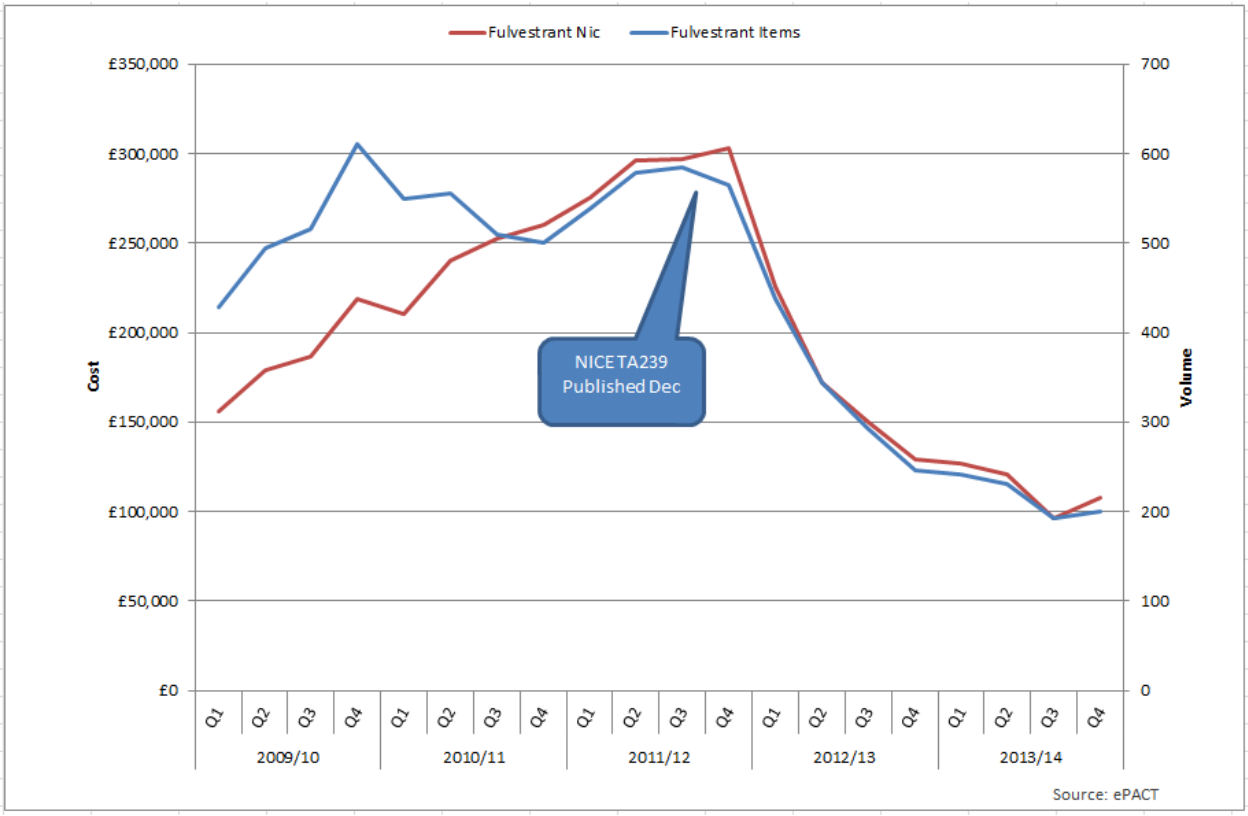


Figure 2 Cost and volume of fulvestrant prescribed in hospitals and dispensed in the community in England between March 2009 and March 2014.



2. Implementation studies from published literature

Nothing to report from the uptake database website.

3. Qualitative input from the field team

The implementation field team have not recorded any feedback in relation to this guidance.

4. Implementation studies from shared learning

A search of the shared learning website highlighted no examples of TA239 being implemented.

Appendix A: Healthcare activity data definitions

ePACT

Prescribing analysis and cost tool system

This information comes from the electronic prescribing analysis and cost tool (ePACT) system, which covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Services Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions dispensed in 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.