NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA240; Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer, and TA242; Cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy

TA240 was terminated because no submission was received, and the termination advice was issued in December 2011. Therefore, there was no review date for TA240. There is an ongoing MTA-Review which already includes a partial update of TA240 for first-line treatment.

TA242 guidance was issued in January 2012. The review date for this guidance is January 2015.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remits

TA240

To appraise the clinical and cost effectiveness of panitumumab in combination with chemotherapy within its licensed indication for the treatment of metastatic colorectal cancer.

TA242

To appraise the clinical and cost effectiveness of cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) within their licensed indications for the treatment of metastatic colorectal cancer after first-line chemotherapy.

3. Current guidance

TA240

NICE is unable to recommend the use in the NHS of panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer because no evidence submission was received from the manufacturer or sponsor of the technology.

This appraisal relates to the treatment of wild-type KRAS metastatic colorectal cancer for first-line treatment in combination with FOLFOX, and for second-line treatment in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

TA242

Updates and replaces TA150 (June 2008) and updates and replaces recommendations in TA118 (January 2007) on the use of cetuximab for the treatment of colorectal cancer that has progressed after first-line chemotherapy.

1.1 Cetuximab monotherapy or combination chemotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.

1.2 Bevacizumab in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.

1.3 Panitumumab monotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.

1.4 People currently receiving cetuximab monotherapy or combination chemotherapy, bevacizumab in combination with non-oxaliplatin chemotherapy, or panitumumab monotherapy for the treatment of metastatic colorectal cancer that has progressed after first-line chemotherapy should have the option to continue treatment until they and their clinician consider it appropriate to stop.

4. Rationale[1]

No new evidence that warrants a review of TA240 or TA242 has been identified. The change in the marketing authorisation for panitumumab is unlikely to materially impact on the cost effectiveness. For cetuximab, the implications of the licence restriction on the cost effectiveness in second line treatment are unknown because the licence change is based on studies of first-line treatment. The price of all 3 drugs has not changed since the original appraisal. It is therefore recommended that TA240 and TA242 are moved to the static list. NICE will reflect the revised marketing authorisations on the landing pages of TA240 and TA242.

5. Implications for other guidance producing programmes

There is an overlap with CG131 (Colorectal cancer: The diagnosis and management of colorectal cancer) published in December 2014, which is due to be reviewed in December 2015. TA242; Cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line

[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

chemotherapy is cross referred to in the guideline and TA240 is listed in the guidance under development section.

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 November 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

Changes in the marketing authorisations for cetuximab and panitumumab

During the development of TA242, cetuximab and panitumumab had marketing authorisations for EGFR-expressing metastatic colorectal cancer with non-mutated (wild-type) **KRAS** exon 2. Since then, excluding additional RAS mutations (KRAS exons 3 and 4, and NRAS exons 2, 3, and 4) was found to improve the efficacy of cetuximab and panitumumab compared with excluding only KRAS mutations. Therefore, the marketing authorisations were restricted to the treatment of wild-type **RAS** tumours.

For panitumumab, the change in the marketing authorisation was based on study 20050203, which evaluated panitumumab plus FOLFOX as a first-line treatment. Additional preliminary results from the 20070509 study that also evaluated the combination with FOLFOX for first-line treatment, and from the pivotal monotherapy trial, 20020408, also provided evidence to support the licence restriction. Of these studies, only study 20020408 investigated panitumumab beyond first-line treatment and it was the key study for panitumumab considered by the Committee in TA242. In study 20050203, overall survival improved by 5.6 months with panitumumab plus FOLFOX compared with FOLFOX alone in patients wild-type RAS tumours (hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.64 to 0.94). In patients with wild-type KRAS tumours, the improvement was by 4.4 months (HR 0.83, 95% CI 0.70 to 0.98).

For cetuximab, the change in the marketing authorisation was based on new biomarker data from 3 RCTs in previously untreated patients with metastatic colorectal cancer (OPUS, CRYSTAL and FIRE III). No data from RCTs for second- or subsequent-line treatment appear to be available. In the OPUS trial, which compared cetuximab plus FOLFOX with FOLFOX alone, the odds ratio for tumour response was more favourable in the RAS wild type compared with KRAS wild type (3.46 [95% CI 1.37 to 8.71] and 2.55 [95% CI 1.38 to 4.72] respectively).

Further details on the results of the biomarker analyses are the European Public Assessment Reports for panitumumab and cetuximab.

List prices

The price of all 3 drugs has not changed since the original appraisal.

Cetuximab (TA242)

The key effectiveness studies for cetuximab in previously treated metastatic colorectal cancer are CO.17, BOND, MABEL and EPIC. All of these studies were available to the Committee in TA242, and no retrospective analyses of the effectiveness in patients with wild-type RAS tumours have been published. This review did not identify new phase III randomised controlled trials (RCTs) for cetuximab, either as monotherapy or in combination with irinotecan-based chemotherapy, in patients who have been previously treated with chemotherapy. Therefore, the recommendations for cetuximab in TA242 are unlikely to change.

Panitumumab (TA240 and TA242)

Monotherapy (TA242)

This review identified a study that presented 3 post hoc analyses of the 20020408 RCT (third- and subsequent-line panitumumab monotherapy) to approximate the treatment effect of panitumumab on overall survival after adjusting for crossover (Poulin-Costello et al., 2013). This study reported differences in median overall survival adjusted for crossover between 2.0 and 3.7 months in favour of panitumumab over best supportive care. These are similar to the crossover-adjusted estimates considered by the Committee in TA242 (2.74–3.13 months). Given that the most plausible ICER in TA 242 for panitumumab in patients with KRAS wild-type tumours was between £110,000 and £150,000 per QALY gained, the improved benefit of panitumumab in patients with RAS wild-type tumours is unlikely to generate much more QALY gains to render panitumumab cost effective.

This review also identified an RCT evaluating the survival benefit of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory wild-type KRAS metastatic colorectal cancer (NCT01412957). However, no results could be retrieved for this trial, and the trial does not include the precise patient population for which this drug is currently licensed.

In combination with FOLFIRI (TA240)

This review did not identify new evidence of substantial nature for panitumumab plus FOLFIRI as a second-line treatment for patients with wild-type RAS metastatic colorectal cancer who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

Bevacizumab (TA242)

During the development of TA242, the Committee was aware that a phase II clinical trial (SPIRITT) comparing bevacizumab plus FOLFIRI with panitumumab plus FOLFIRI after first-line treatment was under way, and noted that the results of this trial should be considered in any future review decision for this appraisal.

In SPIRITT, 182 patients with wild-type KRAS metastatic colorectal cancer were randomised 1:1 to either bevacizumab plus FOLFIRI or panitumumab plus FOLFIRI. Progression-free survival and overall survival were not statistically different between the 2 treatment groups (hazard ratios [HRs] 1.01 [95% confidence interval {CI} 0.68 to 1.49] and 1.06 [95% CI 0.75 to 1.49] respectively).

The population specified in the scope for TA242 related to people with metastatic colorectal cancer whose disease had progressed after first-line chemotherapy. However, SPIRITT included patients previously treated with a first-line bevacizumab plus oxaliplatin-based chemotherapy regimen. Therefore, it is unknown how the results of SPIRITT would differ for patients who had previously received chemotherapy without bevacizumab. Furthermore, patients in SPIRITT had wild-type KRAS tumours, which is not the same as the patient population for which panitumumab is currently licensed.

Overall, the evidence generated by SPIRITT was not considered to be sufficiently relevant and robust to warrant its consideration in the context of an appraisal review. In TA242, it had not been possible to confirm by how much bevacizumab in combination with non-oxaliplatin (fluoropyrimide-based) chemotherapy would extend life when used second line, and therefore no cost-effectiveness evidence for bevacizumab had been presented. The Committee felt that it was unlikely that bevacizumab would be a cost-effective treatment for people with metastatic colorectal cancer who had received first-line therapy based on conclusions reached in previous NICE technology appraisals of bevacizumab, and it could not justify any positive recommendation for bevacizumab in TA242. This conclusion is unlikely to be affected by the evidence from SPIRITT.

Conclusion

No new evidence that warrants a review of TA240 or TA242 has been identified. The change in the marketing authorisation for panitumumab is unlikely to materially impact on the treatment's cost effectiveness. For cetuximab, it would be difficult to fully assess the implications of the licence restriction from the available data. The price of all 3 drugs has not changed since the original appraisal. It is therefore recommended that TA240 and TA242 are moved to the static list.

NICE will reflect the revised marketing authorisations on the landing pages of TA240 and TA242 with the following text:

TA240:

Since the publication of TA240, the population in the marketing authorisation for panitumumab has been revised from 'patients with wild-type KRAS metastatic colorectal cancer' to 'patients with wild-type RAS metastatic colorectal cancer'

TA242:

Since the publication of TA242 the populations in the marketing authorisation has been revised as follows

Panitumumab: from 'patients with wild-type KRAS metastatic colorectal cancer' to 'patients with wild-type RAS metastatic colorectal cancer'

Cetuximab: from 'patients with EGFR-expressing metastatic colorectal cancer with non-mutated (wild-type) KRAS' to 'patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer'

8. Implementation

A submission from Implementation is included in Appendix 3.

The Hospital Pharmacy Audit Index data provided for cetuximab relates to the indications for which NICE has issued positive recommendations, and so does not include the indication for which cetuximab was appraised in TA242.

9. Equality issues

The Committee heard that people with colorectal cancer in England are becoming increasingly worried about what they perceive to be unequal access to treatment with biological drugs, which are currently only provided to some patients through the Cancer Drugs Fund.

GE paper sign off: Elisabeth George, Associate Director, 15/12/2014

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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

Colorectal cancer pathway.

Quality standard for colorectal cancer. QS20. Published: August 2012.

Colorectal cancer: the diagnosis and management of colorectal cancer. Clinical Guideline. CG131. Published: November 2011, updated December 2014. Review date: December 2015.

Improving outcomes in colorectal cancer. Cancer Service Guidance. Published: June 2004.

Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy. Technology Appraisal, TA307. Published: March 2014. Review date: August 2016.

Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer. Technology Appraisal, TA212. Published: December 2010. Review date: May 2013. Review decision: add to static list.

In progress

Colorectal cancer: The organisation and management of services for early rectal cancer and the arrangement of services for the management of bowel obstruction caused by colon cancer (update). Expected publication: December 2014.

Suspended/terminated

Regorafenib for the treatment of metastatic colorectal cancer following prior treatment for metastatic disease. Technology Appraisal, ID593. Status: suspended as the manufacturer is unable to make a submission at this time (August 2013).

Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Indication Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum **Cost** The price of a 100-mg vial is £242.66, and a 400-mg vial is £924.40 (excluding VAT; BNF61)	**Indication** Unchanged Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum Source: SPC (27 October 2014) **Cost** 100-mg vial = £242.66 400-mg vial = £924.40 Source: BNF (October 2014)
Indications Cetuximab for the treatment of patients with EGFR-expressing, *KRAS* wild-type metastatic colorectal cancer, in combination with irinotecan-based chemotherapy or FOLFOX or as a single agent in patients whose disease has failed to respond to oxaliplatin and irinotecan-based therapy, and who are intolerant to irinotecan. **Cost** The list price of a 20-ml vial (100-mg) is £178.10, and a 100-ml vial (500-mg) is £890.50 (excluding VAT; BNF61). The manufacturer of cetuximab has agreed with the Department of Health that the price to the NHS will be £136.50 for a 20-ml vial and £682.50 for a 100-ml vial. Because the reduced prices are in the public domain and are available across the NHS, all calculations in the economic model are based on these reduced prices.	**Indications** Indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer • in combination with irinotecan-based chemotherapy, • as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan. Source: SPC (4 August 2014). Amended by EMA in December 2013 **Cost** 20-ml vial = £178.10 100ml vial = £890.50 Source: BNF (October 2014)

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Indications TA240 Panitumumab for the treatment of patients with wild-type KRAS metastatic colorectal cancer in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan) TA242 Panitumumab as a monotherapy for the treatment of patients with EGFR-expressing metastatic colorectal cancer with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens **Cost** The price of a 100-mg vial is £379.29, and a 400-mg vial is £1517.16 (excluding VAT; BNF61).	**Indications** Indicated for the treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC): • in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan). • as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimen Source: SPC (28 May 2014) Amended by EMA in September 2013 **Cost** 5-mL vial = £379.29 20-mL vial = £1517.16 Source: BNF (October 2014)

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
HA-irinotectan (hyaluronic acid irinotecan complex), Alchemia Oncology	Colorectal cancer - [redacted] Phase III clinical trials [redacted]
Etirinotecan pegol (NKTR 102), Nektar Therapeutics	Colorectal cancer - [redacted] Phase III clinical trials [redacted]
MABp1 (Xilonix), XBiotech	Colorectal cancer - [redacted] Phase III clinical trials [redacted]
Nintedanib (BIBF 1120), Boehringer	Colorectal cancer - metastatic, after failure of standard

Drug (manufacturer)	Details (phase of development, expected launch date,)
Ingelheim	chemotherapy Phase III clinical trials [redacted]
PGG glucan (Imprime PGG), Biothera	Colorectal cancer - [redacted] Phase III clinical trials [redacted]
Ramucirumab (cyramza), Eli Lilly	Colorectal cancer - [redacted] Phase III clinical trials [redacted]
TAS-102, Taiho	Colorectal cancer - [redacted] Phase III clinical trials [redacted]

Registered and unpublished trials

Trial name and registration number	Details
Phase III Trial of Irinotecan-Based Chemotherapy Plus Cetuximab (NSC-714692) or Bevacizumab (NSC-704865) as Second-Line Therapy for Patients With Metastatic Colorectal Cancer Who Have Progressed on Bevacizumab With Either FOLFOX, OPTIMOX or XELOX NCT00499369	Status: Terminated Start date: June 2007 Results available
An open-label, multicenter, randomized phase iii study of second-line chemotherapy with or without bevacizumab in metastatic colorectal cancer patients who have received first-line chemotherapy plus bevacizumab NCT00720512	Status: *Active, not recruiting. Record not verified since July 2009* Start date: June 2008 Estimated completion: March 2014

Trial name and registration number	Details
Open-label Randomized, Parallel Group, Phase III, Multicenter Trial Comparing Two Different Sequences of Therapy (Irinotecan/Cetuximab Followed by Fluorouracil/Leucovorin With Oxaliplatin (FOLFOX-4) vs FOLFOX-4 Followed by Irinotecan/Cetuximab) in Metastatic Colorectal Patients Treated With Fluorouracil/Leucovorin With Irinotecan FOLFIRI /Bevacizumab as First Line Chemotherapy NCT01030042 COMETS	Status: *Active, not recruiting. Record not verified since December 2009* Start date: September 2009 Estimated completion: June 2014
Phase II/III Trial of Cetuximab Plus Irinotecan Synchronously/Subsequently in Patients With KRAS Wild-type Metastatic Colorectal Cancer: an Randomized, Open-label, Multicenter, Prospective Study NCT01550055 Shanghai Zhangjiang Biotechnology Limited Company CRC009	Status: ongoing, not recruiting Start date: March 2012 Estimated completion: October 2013
Multi-Line Therapy Trial in Unresectable Wild-Type RAS Metastatic Colorectal Cancer. A GERCOR Randomized Open-label Phase III Study NCT01910610	Status: recruiting Estimated enrolment: 474 Start date: July 2013 Estimated completion: December 2019
A Phase 3, Multicenter, Randomized, Open-label Trial to Evaluate the Survival Benefit of Panitumumab and Best Supportive Care, Compared to Best Supportive Care Alone, in Subjects With Chemorefractory Wild-type KRAS Metastatic Colorectal Cancer NCT01412957	Status: ongoing, not recruiting Estimated enrolment: 377 Start date: September 2011 Estimated completion: September 2015

Trial name and registration number	Details
Sequential treatment strategy for metastatic colorectal cancer: a phase iii prospective randomized multicenter study of chemotherapy (ct) with or without bevacizumab as first-line therapy followed by two phase iii randomized studies of ct alone or ct plus bevacizumab with or without cetuximab as second-line therapy NCT01878422	Status: recruiting Estimated enrolment: 350 Start date: November 2007 Estimated completion: March 2014
A Multinational, Randomized, Phase III Study of XELIRI With/Without Bevacizumab Versus FOLFIRI With/Without Bevacizumab As Second-line Therapy in Patients With Metastatic Colorectal Cancer NCT01996306 AXEPT	Status: recruiting Estimated enrolment: 600 Start date: December 2013 Estimated completion: January 2017

Relevant services covered by NHS England specialised commissioning

Bevacizumab - approved for first line colorectal cancer indications and second line in combination with oxaliplatin-based chemotherapy but not approved for second line in combination with non-oxaliplatin chemotherapy.

Cetuximab - approved for the second or third line treatment of metastatic colorectal cancer with combination chemotherapy where several criteria are met.

Cetuximab - approved for the third or fourth line treatment of metastatic colorectal cancer as a single agent where several criteria are met.

Panitumumab - approved for first line only - not approved for use in any line of therapy after 1st line

Source: NHS England (24 October 2014) National Cancer Drugs Fund List 2.1

See also:

NHS England (2014) Manual for prescribed specialised services 2013/14 - A08 - Specialised Colorectal Services

Additional information

Westwood M, van Asselt T, Ramaekers B et al. (Oct 2014) KRAS mutation testing of tumours in adults with metastatic colorectal cancer: a systematic review and cost-effectiveness analysis. *Health Technology Assessment* 18(62).

References

Poulin-Costello M, Azoulay L, Van CE et al. (2013) An analysis of the treatment effect of panitumumab on overall survival from a phase 3, randomized, controlled, multicenter trial (20020408) in patients with chemotherapy refractory metastatic colorectal cancer. *Targeted Oncology* 8 (2): 127-136.

Appendix 3 – Implementation submission

1. Routine healthcare activity data

1.1. ePACT data

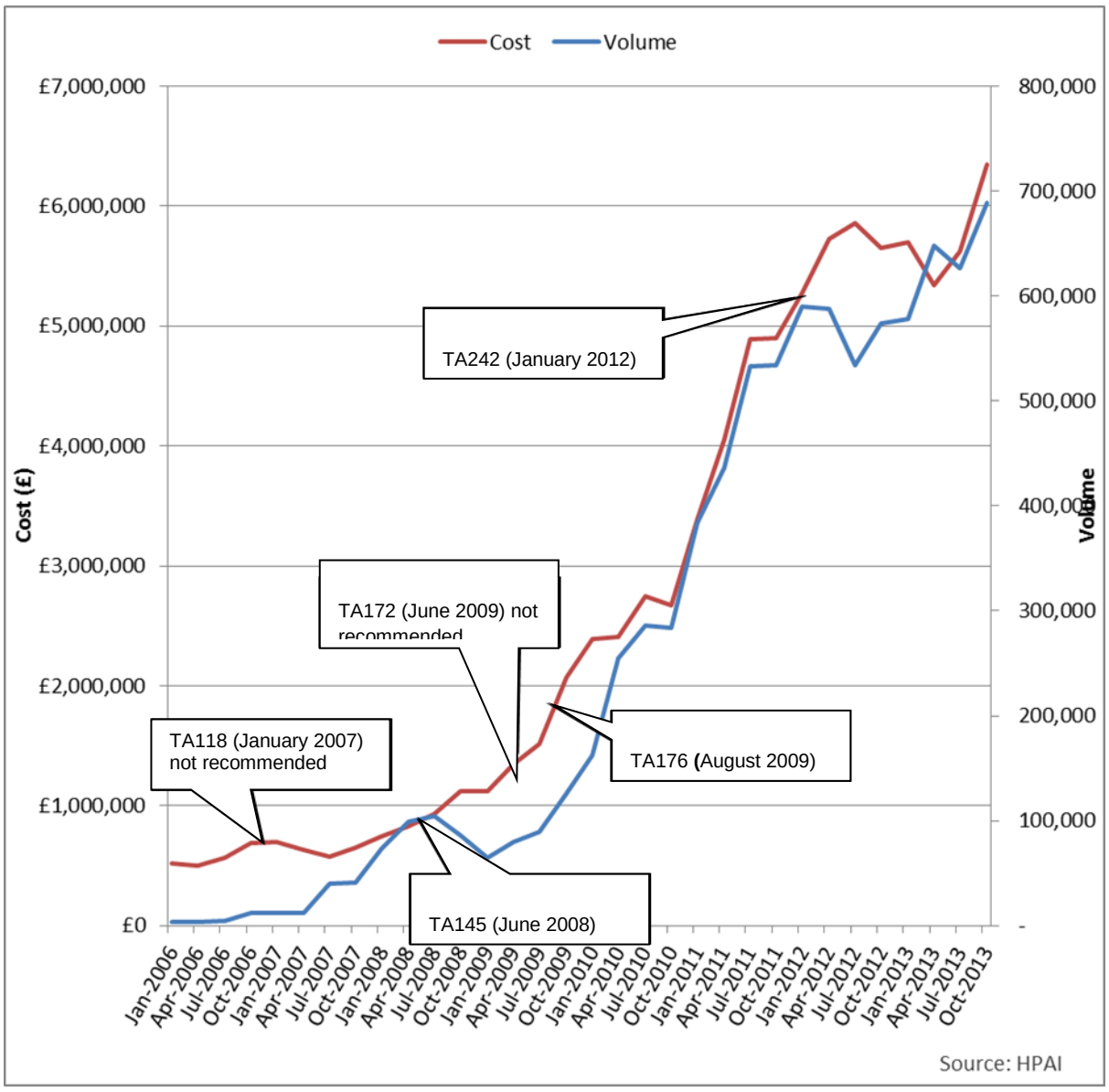
FP10 or FP10HP cost or volume prescribing data in England for Cetuximab, Bevacizumab or Panitumumab was not found for the period 2009 – 2014. This suggests Cetuximab, Bevacizumab and Panitumumab are not prescribed in primary care or by hospitals for dispensing in the community.

1.2. Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index (HPAI) data on the net ingredient cost (NIC) and volume of Cetuximab prescribed and dispensed in hospitals by hospital pharmacies between January 2006 and December 2013 in England. No HPAI data was available for Panitumumab or Bevacizumab as these medicines have not been positively appraised by NICE.

It should be noted the HPAI data available for Cetuximab is as a result of the medicines being positively appraised by NICE in technology appraisals other than the ones reviewed in this report.

Figure 1 Cost and volume of Cetuximab prescribed and dispensed in hospitals in England



1.3. Cancer drug fund notifications

The total number of cancer drug fund (CDF) notifications received by NHS England in 2013/14 for Cetuximab, Bevacizumab and Panitumumab is shown below. Figure 2 shows all CDF notifications for Cetuximab, Bevacizumab and Panitumumab.

Figure 2: Total number of cancer drug fund notifications by drug, all CDF indications in England 2013/14

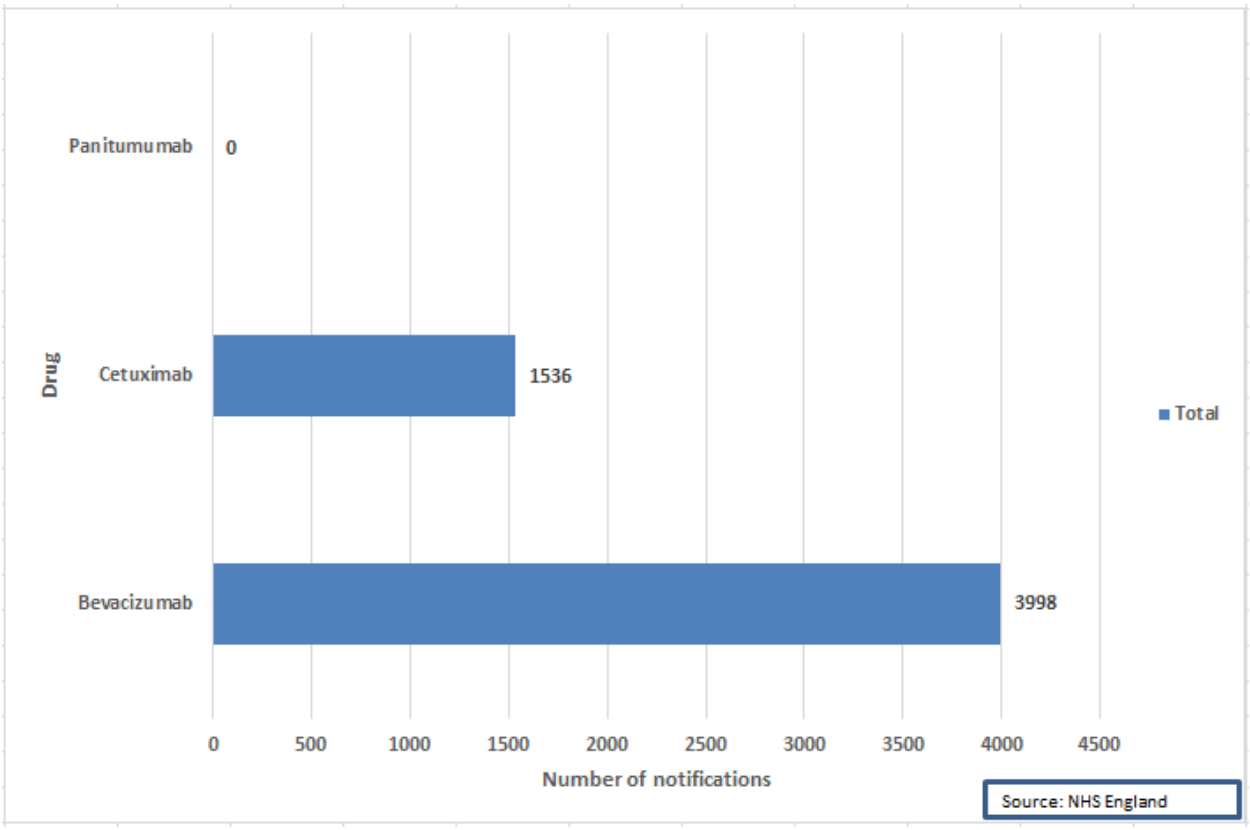


Table 1 shows the total number of CDF notifications received for each drug in 2013/14, split by CDF indication.

Table 1: Number of cancer drug fund notifications by indication, England 2013/14

Drug	CDF indication	Total number of notifications received for each drug 2013/14
Bevacizumab	Treatment of patients with triple negative metastatic breast cancer and/or prior taxane therapy	190
	1st line treatment recurrent or metastatic cervical cancer	20
	The first line treatment of advanced colorectal cancer with a single agent fluoropyramidine in patients assessed as unfit to receive combination oxaliplatin- or irinotecan-based combination chemotherapy	207
	1st line treatment of metastatic colorectal cancer. Only to be administered concurrently with chemotherapy, not as single agent maintenance therapy.	2198
	2nd line treatment of metastatic colorectal cancer in combination with standard chemotherapy in patients who have not previously received bevacizumab. Only to be administered concurrently with chemotherapy, not as single agent maintenance therapy.	397
	3rd line treatment of metastatic colorectal cancer in combination with standard chemotherapy in patients who have not previously received bevacizumab. Only to be administered concurrently with chemotherapy, not as single agent maintenance therapy	95
	The third line treatment of low grade gliomas of childhood	0
	1st line treatment of advanced (stage IIIc/IV) ovarian cancer, suboptimally debulked either at primary or delayed primary (interval) surgery (including peritoneal and fallopian tube cancer) OR unsuitable for debulking surgery	488
	2nd line treatment of platinum sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer (6 or more months after completion of first line chemotherapy)	403
Cetuximab	1st line treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck	205
	Treatment of KRAS wild-type metastatic colorectal cancer in any indication outside of NICE TA176, in patients who have not previously received cetuximab up to progression (Until 13/02/2014).	1175

	1st Line treatment of metastatic coloreactal cancer in combination with the following regimens: FOLFOX4 or FOLFOX6 or OxMdG Chemotherapy (From 13/02/2014)	4
	1st line treatment of metastatic colorectal cancer in combination with Irinotecan based chemotherapy (From 13/02/2014)	54
	2nd or 3rd line treatment of metastatic colorecal cancer in combination with Chemotherapy (From 13/02/2014)	52
	2nd or 3rd line treatment of metastatic colorecal cancer in patients not treated to progression under NICE TA176 (From 13/02/2014)	4
	3rd and subsequent line treatment of metastatic colorecal cancer as a single agent (From 13/02/2014)	34
	3rd and subsequent line treatment of metastatic colorecal cancer as a single agent in patients not treated to progression under NICE TA176 (From 13/02/2014)	8
Panitumumab	1st Line treatment of metastatic coloreactal cancer in combination with the following regimens: FOLFOX4 or FOLFOX6 or OxMdG Chemotherapy	0

2. Implementation studies from published literature

Information is taken from the uptake database website.

Richards, M (2010) Extent and causes of international variation in drug usage: A report for the Secretary of State for Health by Professor Sir Mike Richards CBE
Description: This report looks at medicines usage between countries, using IMS Health data. The WHO defined daily dose or the maximum or prescribed daily dose was used to measure usage. Results rank the UK relative to other countries usage and present calculations showing how close or otherwise the UK is to the average use across groups of other countries. It should be noted that countries other than the UK would not be expected to adhere to NICE guidance making comparisons between countries not possible.

3. Qualitative input from the field team

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

Comment	Created on
Very concerned about the precedent set by refund scheme for Velcade – Director says this is 'the road to destruction' – really threatens the ability to make consistent decisions locally. For example, the pharma manufacturer of cetuximab (NICE did not recommend for colorectal cancer 2007) is now offering fund the first treatment, on the understanding that the PCTs agree to continue funding for 'successful' patients. There is a feeling that 'NICE is too close to the pharma industry', and the Cons PH thought that we should not allow Collaborating t should not work with pharma companies (too much knowledge about the NICE economic model and decision making processes).	15/01/2008 00:00
Interim Cancer Drugs Fund West Midlands fund has been running since October and the level of detail is quite striking. I met yesterday with the pharmacist who sits on their weekly clinical cttee. He commented that: • To date £0.5m of the region's £5m fund has been committed with a further estimated spend of £3.5m "pencilled in". • Applications from clinicians have so far been low – probably due to low awareness • Wherever possible they are using individual funding requests to develop policies for cohorts of patients requiring particular drugs. So far eight of these have been developed. Funding for one drug, bevacizumab for high grade glioma has been turned down. • They estimate that 80% of the fund will be committed on drugs for patient cohorts and 20% for patients who have genuinely individual clinical circumstances • The criteria that patients must fulfil and clinicians must comply with are very specific – see cetuximab example below • All policies are specifically time and cash limited. • The workload associated with the fund is growing and now requires a commitment from the lead pharmacist of 2-3 days per week Please let me know if you need any further details. Links West Midlands Cancer Fund Update http://www.wmsc.nhs.uk/uploaded_media/ICDF%20newsletter%20issue%201.pdf West Midlands Cancer Drugs Fund Policy http://www.wmsc.nhs.uk/uploaded_media/Interim%20Cancer%20Drugs%20Fund%20Policy%20FINAL.pdf West Midlands Interim Cancer Drugs Fund Policy Cetuximab for Advanced Colorectal Cancer http://www.wmsc.nhs.uk/uploaded_media/WM%20ICDF%206%20Cetuximab%20policy%20Oct%202010%20(2).pdf	30/11/2010 22:44
This PCT comes under the Yorks and Humber SCG - discussions with the SCG identified some serious concerns about the risk-sharing principles recently adopted by NICE (Velcade and possibly Lucentis). The Associate Director gave some more examples of pharma companies offering local deals along the same lines, to bypass areas where NICE has not recommended a drug eg lenalimide for mulitple myoloma and cetuximab for colorectal cancer. Details of the scheme have been sent to the IC - forwarded to Andrew Dillon in preparation for a visit to the SCG two weeks afer this visit.	08/04/2008 00:00

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 hospitals or mental health units, and private prescriptions, are not included in PACT data.

Measures of prescribing

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

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

Data limitations (national prescriptions)

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

IMS HEALTH Hospital Pharmacy Audit Index

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

Measures of prescribing

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

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

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

Data limitations

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