Cetuximab, panitumumab and bevacizumab for metastatic colorectal cancer

# Drug utilisation sub-committee (DUSC)

## February 2018

### Abstract

## Purpose

To assess the utilisation of targeted therapies for metastatic colorectal cancer (mCRC) including PBS listed bevacizumab, cetuximab and panitumumab.

## Listings on the Pharmaceutical Benefits Scheme (PBS)

| **First listing date or date of listing amendment(s)** | **Listing details (abridged)** |
| --- | --- |
| 1 July 2009 | Bevacizumab in combination with first-line chemotherapy of a patient with previously untreated metastatic colorectal cancer with a WHO performance status of 0 or 1. |
| 1 September 2011 | Cetuximabas monotherapy or in combination with an irinotecan based therapy, of a patient with a WHO performance status of 2 or less and with KRAS wild type metastatic colorectal cancer after failure of first-line chemotherapy. |
| 1 April 2014 | Panitumumab as monotherapy or in combination with an irinotecan based therapy, of a patient with a WHO performance status of 2 or less and with KRAS wild-type metastatic colorectal cancer after failure of first-line chemotherapy. |
| 1 January 2015 | Amendment to the restrictions for panitumumab and cetuximab to include only patients with rat sarcoma proto-oncogene wild type (*RAS* WT) status rather than Kirsten *RAS* wild type (*KRAS* WT) status. This was in response to evidence which indicated that continuing the current restrictions based on identifying KRAS wild-type patients may expose some of patients to worse health outcomes. |
| 1 February 2015 | The listings for bevacizumab, cetuximab and panitumumab on the Section 100 – Efficient Funding of Chemotherapy (Private Hospital/Private Clinic) Schedule were changed from Authority required to Authority required (STREAMLINED). This was to make the listings consistent with the Authority required (STREAMLINED) items for prescribers in public hospitals. |
| 1 June 2015 | Cetuximab for first-line treatment for metastatic colorectal cancer in combination with first-line chemotherapy.  Bevacizumab in combination with second-line chemotherapy of a patient with RAS wild type metastatic colorectal cancer with a WHO performance status of 0 or 1 after failure of first-line anti-EGFR antibodies. |
| 1 October 2015 | Panitumumab in combination with first-line chemotherapy of a patient with RAS wild-type metastatic colorectal cancer with a WHO performance status of 0 or 1. |

## Data Source / methodology

Data to assess utilisation was obtained from the Department of Human Services (DHS) PBS prescription claims database.

## Key Findings

* The overall utilisation of bevacizumab, cetuximab and panitumumab had stabilised by 2016. In 2016, a total of 5,177 patients were treated for metastatic colorectal cancer with these medicines. Of these, the number of patients first initiating targeted therapy was 2,479.
* The time on treatment with bevacizumab in first-line (~427 days) was longer than the progression-free survival reported in key clinical trials (~340 days). Further, around 11 percent of patients were identified as having been supplied bevacizumab with different chemotherapy partners. These findings suggest that there may have been some use of bevacizumab in patients with progressive disease.
* There were no cases identified where bevacizumab, cetuximab or panitumumab were potentially co-administered with each other.

# Purpose of analysis

To assess the utilisation of targeted therapies for metastatic colorectal cancer (mCRC) including PBS listed bevacizumab, cetuximab and panitumumab.

# Background

## Clinical situation

Colorectal cancer is the second most common cause of cancer-related death in Australia.3 There are over 50,000 Australians living with colorectal cancer with an estimated 16,500 new cases each year.[[1]](#footnote-1) Approximately 20% of people with colorectal cancer have metastatic disease at the time of initial diagnosis.[[2]](#footnote-2) Patients diagnosed with colorectal cancer have about an 8% chance of surviving for five years.3

There are several clinical practice guidelines available for the management of colorectal cancer. These include guides from the [National Comprehensive Cancer Network](http://www.jnccn.org/content/15/3/370.abstract) (NCCN), [National Institute for Health and Care Excellence](https://www.nice.org.uk/guidance/cg131)(NICE) and [European Society for Medical Oncology](http://www.esmo.org/Guidelines/Gastrointestinal-Cancers) (ESMO). At the time of preparing this review, guidelines were being developed by the Cancer Council Australia for the detection, prevention and management of colorectal cancer.

Early stage colorectal cancer can be effectively treated by removing the cancer from the bowel lining or healthy tissue through a surgical procedure known as local resection. Advanced cases may require the removal of a section of the bowel (called a ‘colectomy’). Chemotherapy and radiotherapy may be used to shrink the cancer before surgery. Chemotherapy may also be used after surgery to help kill any remaining cancer cells. Therapies which target the cancerous cells may also be used, discussed further below.

Drug therapy for metastatic colorectal cancer can involve a single drug or a combination of drugs. The choice of therapy depends on several considerations, including a patient’s likely tolerance of the drug(s), prior therapy used and mutations within the tumour.[[3]](#footnote-3) Current therapies have various mechanisms of action to stop or slow tumour growth. These include:

* deoxyribonucleic acid (DNA) repair inhibitors. Disruptions to DNA repair pathways can cause damage to DNA sequences in cells. As a cancer progresses, tumours accumulate more mutations in DNA repair proteins. DNA repair inhibitors interrupt DNA repair to induce cancer cell death.
* Vascular endothelial growth factor (VEGF) inhibitors. By preventing the actions of VEGF, these inhibitors, such as bevacizumab, interrupt the growth of blood vessels that supply nutrients and oxygen to tumours.
* Epidermal growth factor receptor (EGFR) inhibitors. Deficient signally of the EGFR can cause the development of tumours. EGFR inhibitors, such as cetuximab and panitumumab, interrupt signalling errors from the receptor to affect the growth of EGFR-expressing tumours.

The outcomes of drug therapy may also depend on whether a colon cancer has mutations in the rat sarcoma (RAS) oncogene. The RAS oncogene is involved in cell growth and overactive signalling of this gene can cause cancer. Around half of patients with colorectal cancer have the mutant version of the RAS oncogene (Sorich et al., 2015). Identifying mutations in the RAS oncogene has important implications for therapy outcomes as they are a predictor of non-response in some therapies, such as cetuximab and panitumumab.

Panitumumab is used to treat colon cancer in patients whose tumours have no mutation in the RAS genes. For patients who are treated with bevacizumab or cetuximab after receiving prior treatment with another therapy, these drugs are used where the person has a mutation in the RAS wild-type gene.

A [Medicare Benefits Schedule](http://www.mbsonline.gov.au/) (MBS) service is available to undertake the required testing to determine the RAS status (MBS item 73338) to access PBS subsidised cetuximab and panitumumab.

# Therapeutic Goods Administration (TGA) approved indications

**Bevacizumab**

Bevacizumab is registered for use in combination with fluoropyrimidine-based chemotherapy for the treatment of patients with metastatic colorectal cancer.

Bevacizumab is also registered for several other indications, including:

* Locally recurrent or metastatic breast cancer;
* Advanced, metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC);
* Advanced and/or metastatic renal cell cancer;
* Grade IV glioma;
* Ovarian, fallopian tube or primary peritoneal cancer; and
* Cervical cancer.

Further information about the current TGA approved indications for bevacizumab is available from the [Australian Register of Therapeutic Goods.](https://www.tga.gov.au/australian-register-therapeutic-goods)

**Cetuximab**

Cetuximab is indicated for the treatment of patients with EGFR-expressing, RAS wild-type metastatic colorectal cancer:

* in combination with infusional 5-fluorouracil/folinic acid plus irinotecan;
* in combination with irinotecan in patients who are refractory to first-line chemotherapy;
* in first-line in combination with FOLFOX[[4]](#footnote-4); and
* as a single agent in patients who have failed or are intolerant to oxaliplatin-based therapy and irinotecan-based therapy.

Cetuximab is also indicated for squamous cell cancer of the head and neck.

Further information about the current TGA approved indications for cetuximab is available from the [Australian Register of Therapeutic Goods.](https://www.tga.gov.au/australian-register-therapeutic-goods)

**Panitumumab**

Panitumumab is indicated for the treatment of patients with wild-type RAS metastatic colorectal cancer as:

* first line therapy in combination with FOLFOX;
* second line therapy in combination with FOLFIRI[[5]](#footnote-5) for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan); and
* as monotherapy in patients after the failure of standard chemotherapy.

Further information about the current TGA approved indications for panitumumab is available from the [Australian Register of Therapeutic Goods.](https://www.tga.gov.au/australian-register-therapeutic-goods)

# Dosage and administration

The recommended doses and frequencies of administration for bevacizumab, cetuximab and panitumumab according to the approved product information are presented in Table 1.

**Table 1: Dosage and administration of bevacizumab, cetuximab and panitumumab for metastatic colorectal cancer**

| Brand name and sponsor | Product | Dose and frequency of administration |
| --- | --- | --- |
| Avastin, Roche Products Pty Ltd | Bevacizumab | Bevacizumab is administered as an IV infusion. For first-line treatment, the recommended dose is 5 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg of body weight given once every 3 weeks. For second-line treatment, the recommended dose is 10 mg/kg of body weight given every 2 weeks or 15 mg/kg of body weight given once every 3 weeks.  Dose reduction of bevacizumab for adverse events is not recommended. Instead, discontinuation or a break in therapy is recommended. |
| Erbitux, Merck Serono Australia Pty Ltd | Cetuximab | Cetuximab is administered by infusion once a week. The initial dose is 400 mg per m2 body surface area. The recommended dose for subsequent weekly doses is 250 mg per m2 each.  Premedication with an antihistamine and a corticosteroid is recommended prior to infusions.  Dose modifications may be required if a patient experiences infusion-related events of adverse skin reactions. |
| Vectibix, Amgen Australia Pty Limited | Panitumumab | Panitumumab is administered as an infusion. The recommended dose is 6 mg/kg given once every 2 weeks.  Dose modifications may be required if patient experiences infusion-related events of adverse skin reactions. |

Source: Product Information (PI) and Consumer Medicine Information (CMI) available from [the TGA (Product Information)](http://tga.gov.au/hp/information-medicines-pi.htm) and [the TGA (Consumer Medicines Information)](http://www.tga.gov.au/consumers/information-medicines-cmi.htm). Accessed in October 2017.

# PBS listing details (as at October 2017)

Bevacizumab, cetuximab and panitumumab are Authority Required (STREAMLINED) PBS listings. Further details about the individual PBS listings are provided in Appendix 1.

## Restrictions (abridged)

**Bevacizumab**

First-line

Bevacizumab has an Authority Required (STREAMLINED) listing for the treatment of metastatic colorectal cancer in combination with first-line chemotherapy in previously untreated patients. A person must have a WHO performance status of 0 or 1. To receive a continuing supply of bevacizumab, patients must not have progressive disease.

After failure of first-line anti-EGFR antibodies

Bevacizumab has an Authority Required (STREAMLINED) listing for use in combination with second-line chemotherapy after prior treatment with PBS-subsidised first-line anti-EGFR antibodies. To initiate on bevacizumab, a person must have RAS wild-type metastatic colorectal cancer and a WHO performance status of 0 or 1.

**Cetuximab**

First-line

Cetuximab has an Authority Required (STREAMLINED) listing in combination with first-line chemotherapy for patients with previously untreated metastatic colorectal cancer. To access initial therapy with cetuximab, a person must have RAS wild-type metastatic colorectal cancer and a WHO performance status of 0 or 1.

After failure of first-line chemotherapy

Cetuximab has an Authority Required (STREAMLINED) listing for the treatment of metastatic colorectal cancer, either as monotherapy or in combination with chemotherapy, after prior treatment with first-line chemotherapy. A person must have RAS wild-type metastatic colorectal cancer and a WHO performance status of 2 or less.

**Panitumumab**

First-line

Panitumumab has an Authority Required (STREAMLINED) listing for the management of previously untreated metastatic colorectal cancer in combination with first-line chemotherapy. A person must have RAS wild-type metastatic colorectal cancer and a WHO performance status of 0 or 1.

Patients who are intolerant to cetuximab may receive panitumumab. If a person has experienced progressive disease on cetuximab they are not eligible to receive panitumumab.

After failure of first-line chemotherapy

Panitumumab has an Authority Required (STREAMLINED) listing for the treatment of metastatic colorectal cancer, either as monotherapy or in combination with chemotherapy, after prior treatment with first-line chemotherapy. A person must have RAS wild-type metastatic colorectal cancer and a WHO performance status of 2 or less.

Patients who are intolerant to cetuximab are eligible to receive panitumumab. However, a person with progressive disease on cetuximab is ineligible for panitumumab.

For further details of the current PBS listings refer to the [PBS website](http://www.pbs.gov.au/pbs/home).

## Listings on the Pharmaceutical Benefits Scheme (PBS)

**Table 2: Summary of PBS listings for bevacizumab, cetuximab and panitumumab**

| **First listing date or date of listing amendment(s)** | **Listing details (abridged)** |
| --- | --- |
| 1 July 2009 | Bevacizumab in combination with first-line chemotherapy of a patient with previously untreated metastatic colorectal cancer with a WHO performance status of 0 or 1. |
| 1 September 2011 | Cetuximabas monotherapy or in combination with an irinotecan based therapy, of a patient with a WHO performance status of 2 or less and with KRAS wild type metastatic colorectal cancer after failure of first-line chemotherapy. |
| 1 April 2014 | Panitumumab as monotherapy or in combination with an irinotecan based therapy, of a patient with a WHO performance status of 2 or less and with KRAS wild-type metastatic colorectal cancer after failure of first-line chemotherapy. |
| 1 January 2015 | Amendment to the restrictions for panitumumab and cetuximab to include only patients with rat sarcoma proto-oncogene wild type (*RAS* WT) status rather than Kirsten *RAS* wild type (*KRAS* WT) status. This was in response to evidence which indicated that continuing the current restrictions based on identifying KRAS wild-type patients may expose some of patients to worse health outcomes. |
| 1 February 2015 | The listings for bevacizumab, cetuximab and panitumumab on the Section 100 – Efficient Funding of Chemotherapy (Private Hospital/Private Clinic) Schedule were changed from Authority required to Authority required (STREAMLINED). This was to make the listings consistent with the Authority required (STREAMLINED) items for prescribers in public hospitals. |
| 1 June 2015 | Cetuximab for first-line treatment for metastatic colorectal cancer in combination with first-line chemotherapy.  Bevacizumab in combination with second-line chemotherapy of a patient with RAS wild type metastatic colorectal cancer with a WHO performance status of 0 or 1 after failure of first-line anti-EGFR antibodies. |
| 1 October 2015 | Panitumumab in combination with first-line chemotherapy of a patient with RAS wild-type metastatic colorectal cancer with a WHO performance status of 0 or 1. |

Current PBS listing details are available from the [PBS website](http://www.pbs.gov.au/pbs/home).

# Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

The recommendations for each drug are presented separately in the following order: bevacizumab, cetuximab and panitumumab.

## Bevacizumab

In March 2008, PBAC rejected a submission for bevacizumab for use in combination with fluorouracil, folinic acid and irinotecan or fluorouracil and folinic acid, for the treatment of patients with metastatic colorectal cancer. PBAC was concerned about the leakage of bevacizumab for use as a single agent and into second-line in patients with a poorer performance status. For further details refer to the [Public Summary Document from the March 2008 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-03/pbac-psd-bevacizumab-mar08).

In July 2008, PBAC recommended bevacizumab in combination with first-line chemotherapy, for people with previously untreated metastatic colorectal cancer with a WHO performance status of 0 or 1. For further details refer to the [Public Summary Document from the July 2008 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-07/pbac-psd-bevacizumab-july08).

## Cetuximab

In March 2005, PBAC rejected a submission for cetuximab in combination with irinotecan for the treatment of epidermal growth factor receptor (EGFR) expressing mCRC because of uncertain clinical benefit and uncertain but unacceptable cost-effectiveness. The listing was proposed as second-line after failure to irinotecan based therapy or failure or unsuitable for oxaliplatin based therapy,

The November 2005 submission sought to list cetuximab in combination with irinotecan for patients who have failed standard chemotherapeutic treatments. The PBAC accepted the proposed comparator of “usual care” consisting of best supportive care (BSC) and chemotherapy agents used third-line at the time of the application, including capecitabine, 5-FU (+ mitomycin C) and raltitrexed. The comparative toxicity of cetuximab plus irinotecan was uncertain. PBAC considered that the analysis of cost-effectiveness was biased in favour of cetuximab. For further details refer to the [Public Summary Document from the November 2005 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2005-11/cetuximab).

**Committee-in-confidence**

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In November 2008, a submission seeking the listing of cetuximab as a third-line treatment of mCRC in patients whose tumour has wild type K-RAS was rejected. PBAC considered the extent of survival benefit over best supportive care was uncertain and hence the resultant high cost effectiveness ratio was highly uncertain. PBAC considered that it was possible that K-RAS was a treatment effect modifier but there was uncertainty about the predictive and prognostic role of K-RAS mutations. For further details refer to the [Public Summary Document from the November 2008 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-11/pbac-psd-cetuximab-nov08).

The March 2009 minor re-submission, which sought to address the PBAC’s concerns about K-RAS diagnostic testing and the economic evaluation for the November 2008 submission, was rejected. The extent of overall survival benefit of cetuximab over best supportive care in the KRAS sub-group remained uncertain because: it was based on a post-hoc analysis; and the treatment effect was extrapolated beyond the trial period (14 months to 5 years). The potential impact of false positive and false negative outcomes to the economic evaluation was considered to be unknown because of a lack of data on the sensitivity and specificity of the available K-RAS tests. For further details refer to the [Public Summary Document from the March 2009 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2009-03/pbac-psd-cetuximab-march09).

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**End committee-in-confidence**

In March 2010, PBAC rejected a submission for cetuximab in combination with first-line chemotherapy for the first-line treatment of patients with K-RAS wild-type mCRC. For further details refer to the [Public Summary Document from the March 2010 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2010-03/pbac-psd-cetuximab-mar-10).

In July 2010, PBAC recommended listing cetuximab on the PBS as an Authority Required listing as monotherapy or in combination with an irinotecan based therapy, for a person with a WHO performance status of 2 or less and with K-RAS wild type metastatic colorectal cancer after failure of first-line chemotherapy. The PBAC agreed that there was no clinical benefit of treatment with combination cetuximab and bevacizumab based on randomised control trial (RCT) evidence.

In November 2014, cetuximab was recommended for the first-line treatment of mCRC on a cost-minimisation basis with bevacizumab. The recommended equi-effective doses were 8,356 mg cetuximab vs. 4,229 mg bevacizumab.

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**End committee-in-confidence**

## Panitumumab

In November 2008, PBAC rejected a submission for panitumumab for treatment of K-RAS wild type mCRC after failure of treatment with a fluoropyrimidine, irinotecan and oxaliplatin. This was on the basis of uncertainty about the extent of clinical benefit over best supportive care, both in terms of progression free and overall survival, and because of the resultant high and highly uncertain cost effectiveness ratio. For further details refer to the [Public Summary Document from the November 2008 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-11/pbac-psd-panitumumab-nov08).

In March 2013, PBAC considered a submission for panitumumab which sought the following listings:

* Treatment, as monotherapy or in combination with FOLFIRI, of a person with a WHO performance status of 2 or less and with a K-RAS wild-type metastatic colorectal cancer after failure of first-line chemotherapy; and
* Treatment, in combination with FOLFOX, of a person with a WHO performance status of 2 or less with previously untreated K-RAS wild-type metastatic colorectal cancer where treatment with bevacizumab is unsuitable.

The PBAC rejected the request for first-line treatment because of inadequate clinical trial data to support this listing. The PBAC recommended the later-line setting as a monotherapy or in combination with an irinotecan based therapy. This listing was recommended on the basis of the comparison against cetuximab, but with the price for panitumumab to be lower than cetuximab’s price as PBAC was not convinced that panitumumab was non-inferior to cetuximab. For further details refer to the [Public Summary Document from the March 2013 PBAC meeting.](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-03/panitumumab)

In November 2013, the PBAC recommended listing of panitumumab under the Section 100 Efficient Funding of Chemotherapy Program for the later-line treatment of K-RAS wild-type mCRC on a cost-minimisation basis compared with cetuximab. The PBAC considered that this recommendation should replace the recommendation made at its meeting in March 2013. The equi-effective doses are panitumumab 6 mg/kg every two weeks and cetuximab 250 mg/m2 weekly, following an initial loading dose of 400 mg/m2. For further details refer to the [Public Summary Document from the November 2013 PBAC meeting.](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-11/panitumumab)

For the July 2014 panitumumab submission, PBAC made the following recommendations:

* To change the later-line listings from KRAS wild-type to RAS wild-type. This amendment was made to the listings from 1 January 2015; and
* The request to list panitumumab for the first-line treatment of RAS wild-type mCRC was rejected because of uncertainty around the clinical benefit.

For further details refer to the [Public Summary Document from the July 2014 PBAC meeting.](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-07/panitumumab-psd-07-2014)

In March 2015, the PBAC recommended the first-line listing of panitumumab, for the treatment of RAS wild-type metastatic colorectal on a cost minimisation basis with cetuximab. The equi-effective doses are panitumumab 6 mg/kg every two weeks and cetuximab 250 mg/m2 weekly, following an initial loading dose of 400 mg/m2. This listing was expected to be cost neutral to the Commonwealth. [Public Summary Document from the March 2015 PBAC meeting.](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2015-03/panitumumab-vectibix-psd-03-2015)

The restrictions for cetuximab were revised from 1 June 2015 to also allow its use in combination with non-irinotecan based chemotherapy regimens.

# Previous reviews by the DUSC

DUSC previously reviewed the utilisation of bevacizumab and cetuximab for mCRC at its June 2013 meeting. The review found the utilisation of bevacizumab was similar to predicted at the time of listing. The total number of patients treated with cetuximab was lower than predicted. This may have been due to some eligible patients being enrolled in clinical trials or access programs for alternate therapies.

# Methods

## Data extraction

PBS prescription data were extracted for mCRC listings for bevacizumab, cetuximab and panitumumab from 1 January 2009 (the first listing date of bevacizumab) to 31 July 2017. Based on common chemotherapy drug regimens used to treat colorectal cancer, PBS prescription data was also extracted for irinotecan, capecitabine, oxaliplatin, fluorouracil, folinic acid and leucovorin from 1 January 2006 to 31 July 2017. This gave a look back period of at least three years before the first listing of bevacizumab from July 2009 to identify chemotherapy regimens supplied before bevacizumab, cetuximab or panitumumab. The data extractions were based on the date of supply. The date of processing of PBS prescriptions may differ from the date of supply. As such, there may be differences in the data reported by date of supply or processing (such as that available publicly available from the [DHS Medicare website](https://www.humanservices.gov.au/corporate/statistical-information-and-data/medicare-statistics#a2)).

## Number of PBS patients and number of infusions

PBS prescription data were used to determine the number of infusions supplied and to count the number of patients.

Patient counts were obtained for both incident (new to treatment) and prevalent (number treated in each time period, i.e. year or quarter). If doses are delayed, prevalent patients may not receive a supply every month. As such, patient numbers were presented quarterly as it was expected most patients would receive a supply at least once each quarter.

The number of infusions of bevacizumab, cetuximab or panitumumab is influenced by the frequency of their administration. Bevacizumab may be administered once every two or three weeks (Table 1). Cetuximab is recommended to be administered once a week, however an analysis of the time to re-supply suggests it may have also been administered every two weeks in some cases (see Appendix 2, Figure A2.1). As such, caution is required when interpreting the number of infusions as the trends are subject to variation due to the differences in the frequency of administration. A supplementary analysis of the number of infusions is presented in Appendix 3.

[Revised arrangements for the efficient funding of chemotherapy drugs (EFC)](http://www.pbs.gov.au/info/publication/factsheets/shared/revised-arrangements-for-chemotherapy) were introduced from 1 December 2011. Under these arrangements, prescribers write prescriptions with a specific dose, usually in milligrams, and approved suppliers/pharmacies dispense the drug using the combination of vials that most efficiently makes up the required dose for the patient. That is, a prescription is for the infusion comprising of vials which may have differing strengths and sizes. Before the EFC, a prescription related to a vial or multiple vials of a particular strength and size. In order to compare the utilisation before and after the introduction of the EFC, the pre EFC data consisting of all vials supplied on a single day was converted to infusions. This was done by identifying where a patient got more than one supply of a medicine on the same day. Multiple supplies on the same day were counted as one infusion.

Prescriptions for the targeted therapies were classified as either being for therapy in first-line, second-line or after second-line as described below.

## Drug regimens and drug sequence analyses

The median time between supplies for bevacizumab, cetuximab or panitumumab and the chemotherapy agents was obtained to inform assumptions around medicine coverage times to identify co-administered drugs. The distributions for the time between supplies for each drug are provided in Appendix 2. Bevacizumab and panitumumab were found to have the longest time between supplies (median of 14 days). The median time between supplies was less than 14 days for the chemotherapy drugs with the exception of folinic acid which was 62 days. To allow for potential treatment breaks, it was assumed that the period of a potential treatment break was three times the median days between supplies (i.e. 42 days for all drugs except folinic acid which was assumed to be 186 days). Except for folinic acid (leucovorin), a drug was assumed to be co-administered with another drug if its date of supply was within 42 days of the previous or next supply. The co-administration of folinic acid with other drugs was assumed if its supply occurred within 186 days before or after the date of supply of another drug. The chemotherapies were classified into the following drug regimens: irinotecan + fluorouracil + folinic acid (FOLFIRI); folinic acid + fluorouracil + oxaliplatin (FOLFOX); fluorouracil + leucovorin (FU-LV); irinotecan + capecitabine (XELIRI); and oxaliplatin + capecitabine (XELOX).

After classifying the chemotherapies into regimens, an analysis of the sequence of drug regimens supplied to patients who first initiated on bevacizumab, cetuximab or panitumumab was undertaken in two patient cohorts for 2014 and 2016. The 2014 cohort was selected to capture the impact of panitumumab’s listing as a second-line treatment from April 2014. The 2016 cohort was chosen to include the impact of cetuximab and panitumumab’s listings as a first-line treatment for mCRC from June and October 2015, respectively. For both cohorts, the follow-up period was to 31 July 2017.

The prescription records for each patient were sorted by the date of supply to obtain the temporal sequence of drug regimens. For each prescription record, the time between a given regimen relative to the last and next regimen was obtained.

The supply of bevacizumab, cetuximab or panitumumab was classified as being for monotherapy if: no other supplies of a chemotherapy regimen or alternative targeted drug were detected within 42 days before or 42 days after the date of supply of a given prescription of the single targeted drug; and there was a sequential supply of more than one prescription for a targeted drug or a chemotherapy regimen.

The co-administration of bevacizumab, cetuximab or panitumumab with a chemotherapy regimen was assumed if a regimen was supplied within 42 days before or within 42 days after the supply of a targeted drug.

An analysis was undertaken to investigate whether there was any co-administration among bevacizumab, cetuximab and panitumumab. An initial examination was done to find if an alternative targeted drug was supplied within 42 days before or 42 days after the supply date for another targeted drug which may indicate co-administration or switching between therapies. No cases of co-administration were found.

## Length of treatment

The length of treatment of the targeted therapies was derived using the Kaplan-Meier method. Treatment length was determined accounting for treatment breaks and excluding treatment breaks. A treatment break was assumed if there was a gap of more than three times the median time to resupply (i.e. 42 days as described above). A patient was considered to be continuing on therapy (i.e. censored in the Kaplan-Meier analysis) if the date of their last prescription was within three times the median time to resupply of the analysis end date (i.e. 31 July 2017). Otherwise the patient was considered to have ceased treatment.

A cohort of first-time initiators to either bevacizumab, cetuximab or panitumumab between 1 January 2014 and 31 December 2014 was selected. This cohort was selected to provide an adequate time period to follow patients through their sequences of therapy. The supply of any targeted drug to this patient cohort was followed up to 31 July 2017. The time on treatment for the first drug supplied, and any second or third drug supplied, was examined. A separate analysis was also done for the time on bevacizumab in first-line.

# Results

## Analysis of drug utilisation

### *Number of initiating and prevalent PBS patients*

The number of newly treated patients remained relatively stable over time (Figure 1, Table 3). As a result, there was a plateau in the total number of patients supplied with bevacizumab, cetuximab or panitumumab between Quarter 1 2016 to Quarter 2 2017 (Figure 1).

**Figure 1: Number of incident and prevalent patients by quarter who received a supply of bevacizumab, cetuximab or panitumumab for mCRC**

**Table 3: Number of incident and prevalent patients who received a supply of bevacizumab, cetuximab or panitumumab by year**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient group** | **2009a** | **2010** | **2011** | **2012** | **2013** | **2014** | **2015** | **2016** | **2017b** |
| Incidentc | 1,237 | 2,111 | 2,221 | 2,330 | 2,406 | 2,430 | 2,552 | 2,479 | 1,723 |
| Prevalent | 1,237 | 2,982 | 3,707 | 4,366 | 4,672 | 4,920 | 5,115 | 5,177 | 4,405 |

Note:

a Part-year data from 1 July 2009 (i.e. first listing date for bevacizumab) to 31 December 2009.

b Part-year data from 1 January 2017 to 31 July 2017.

c First ever supply of subsidised bevacizumab, cetuximab or panitumumab.

Cetuximab and panitumumab were listed as first-line treatments for mCRC from June 2015 and October 2015, respectively. Since these listings, most patients had continued to be first initiated on bevacizumab (Figure 2).

**Figure 2: Number of first-time initiators supplied with bevacizumab, cetuximab or panitumumab for mCRC**

Of the 2,479 initiators, three-quarters (75.4%) were supplied bevacizumab as first-line therapy. First-line cetuximab was used in 18.8% of patients with around 6% of patients receiving panitumumab in first-line.

Across all lines of therapy, the majority of patients were supplied bevacizumab compared to cetuximab and panitumumab (Figure 3).

**Figure 3: Number of patients supplied with bevacizumab, cetuximab or panitumumab for mCRC by line of targeted therapy**

Following the listing of panitumumab for treatment after failure of first-line therapy in April 2014, there was a small amount of growth in the use of second-line targeted therapies (ranging from 0.6 percent and 3.8 percent per quarter between Quarters 2 to 4 in 2014, Figure 3). Between Quarter 1 2015 to Quarter 2 2017, the average growth per quarter was minimal (0.1%), (Figure 3).

After the listing of panitumumab, the average growth per quarter in the after second-line setting was 10.6%. However, the number of patients supplied a targeted therapy after second-line was small (e.g. 143 patients in Quarter 2 2017) relative to earlier lines of therapy (Figure 3).

In Quarter 2 of 2017, the proportion of patients on first-, second- and later lines of targeted therapy was 81 percent, 17 percent and 2 percent, respectively.

### *Time on targeted therapy with bevacizumab, cetuximab and panitumumab*

The time on targeted drugs by line of therapy was examined in a cohort of patients first initiating on either bevacizumab, cetuximab or panitumumab in 2014. Table 4 shows the number of initiations to each targeted drug by line of therapy for the 2014 cohort.

Table 4. Drug initiations by line of therapy

| **Analysis** | **Drug group** | **n** | **Proportion** |
| --- | --- | --- | --- |
| First-line | Bevacizumab | 2,132 | 87.7% |
| (Total initiators = 2,430) | Cetuximab | 266 | 10.9% |
|  | Panitumumab | 32 | 1.3% |
| Second-line | Bevacizumab | 50 | 7.9% |
| (Total initiators = 634) | Cetuximab | 452 | 71.3% |
|  | Panitumumab | 132 | 20.8% |
| Third-line | Cetuximab | 7 | 18.9% |
| (Total initiators = 38) | Panitumumab | 30 | 81.1% |

Of the 2,430 initiators in 2014, 26% were supplied a second-line target drug and 2% were supplied a third-line target drug (Table 4).

For all episodes of targeted therapy, the median time on treatment, including breaks in therapy, was 517 days (Table 5). Compared to the initiators who had a treatment break (n=1,193), the patient group without a treatment break (n=1,237) experienced a higher number of failures (1,222 vs. 1,033, respectively) and had a shorter time on treatment (median 91 days). Patients may have discontinued treatment without further re-treatment due to mortality.

Table 5. Time on treatment including treatment breaks

| **Analysis** | **n** | **Mean** | **Median time on treatment (days)** | **Lower CI**  **(days)** | **Upper CI**  **(days)** |
| --- | --- | --- | --- | --- | --- |
| All episodes of targeted therapy | 2,430 | 587 | 517 | 483 | 543 |
| First-line | 2,430 | 512 | 409 | 385 | 434 |
| Second-line | 634 | 198 | 129 | 107 | 145 |
| Third-line | 37 | 170 | 147 | 73 | 218 |

For first-line treatment, where the majority of patients were treated with a drug regimen containing bevacizumab (Table 6), the median time on treatment was 409 days (Table 5). When examining time on bevacizumab alone in first-line, the median time on treatment including breaks in therapy, was 427 days (95%CI: 399, 455 days). The time on second- and third- line treatment was likely to have been slightly underestimated as a small proportion of patients (approximately 7%) were identified as continuing on therapy after the analysis end date. Further, the analysis of time on third-line therapy was only informed by a small number of patients (Table 5). Based on the available data, the median time on later-line therapy ranged between around 130-150 days (Table 5).

### *Utilisation of drug regimens*

An attempt was made to identify chemotherapy regimens and to analyse the sequence of drug therapies. Due to the difficulties in identifying the supply of chemotherapy regimens using PBS claims data, some drug regimens were not readily detected. As such, the DUSC requested that the results for these analyses be removed from the report. Refer to the ‘DUSC consideration’ section for further information.

# Discussion

## Treatment uptake

The number of initiators on bevacizumab, cetuximab or panitumumab for mCRC remained relatively stable at around 2,400 to 2,500 patients between 2013 and 2016 (Table 3, Figure 1). Consequently, the total number of patients treated with these drugs had plateaued to around 5,100 in 2015 and 2016 (Table 3, Figure 1).

There was a lack of data on the incidence and prevalence of mCRC in Australia to assess changes in the eligible population within the later period of the analysis. Available projections made by the Australian Institute of Health and Welfare (AIHW) indicated that colorectal cancer was expected to represent the second most commonly diagnosed cancer in Australia by 2017 (AIHW, 2017). Further, the gradual phasing in of the National Bowel Cancer Screening Program[[6]](#footnote-6) over the analysis period may have influenced the rates of diagnosis of colorectal cancer and the number of patients in the various stages of this disease. However, despite the anticipated increase in the number of people diagnosed with colorectal cancer, the growth rate for the utilisation of the PBS listings for bevacizumab, cetuximab or panitumumab declined. These trends may reflect the participation of some patients in clinical trials that may have otherwise been eligible for PBS therapy. There were several clinical trials being conducted in Australia that were recruiting participants at the time of reporting. Examples included the BEACON-CRC Phase 3 trial,[[7]](#footnote-7) the ElevatION CRC-101 Phase 1 trial,[[8]](#footnote-8) and a Phase 1 trial investigating ribociclib in combination with trametinib (Phase 1).[[9]](#footnote-9)

## First initiations to bevacizumab, cetuximab or panitumumab

A patient may not be suitable for a targeted drug for several reasons. Bevacizumab is associated with an increased risk of blood clots with reports of heart attacks and strokes during therapy in a small proportion of patients (up to 4 percent).[[10]](#footnote-10) As a result, bevacizumab may not be recommended for patients over the age of 65 years or who have prior heart conditions.

The decision to first initiate an individual on bevacizumab, cetuximab or panitumumab is also dependant on whether they have a diagnosis of RAS oncogene mutation. The prevalence of RAS mutations occurs in around half of people with mCRC (Peeters et al., 2015; Sorich et al., 2015, Boleij et al. 2016). The proportion of RAS oncogenes that are wild-type is reported to be around 40 percent (Harle et al., 2016).

Available evidence indicates that epidermal growth factor receptor (EGFR) inhibitors, including cetuximab and panitumumab, should only be used to treat mCRC where patients are wild-type for all known RAS-activating loci (Sorich et al., 2015). Access to PBS subsidised cetuximab and panitumumab requires a diagnosis of RAS wild-type status whereas bevacizumab does not have this restriction.

Around 75 percent of patients first initiated on a targeted therapy in 2016 were on drug regimens containing bevacizumab. The lower number of initiators on cetuximab and panitumumab may relate to their restricted use in people with RAS wild-type status only. Cetuximab and panitumumab are also associated with infusion reactions, including skin toxicities and anaphylaxis (NCCN guidelines, 2017, p.382), which may have influenced clinicians’ choice in the use of these drugs. In its recommendation for cetuximab in 2014, the PBAC noted that there was a higher frequency of skin-related adverse events for cetuximab ([Public Summary Document for the November 2014 PBAC meeting](http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2014-11/files/cetuximab-psd-11-2014.pdf)).

The March 2015 recommendation for panitumumab in first-line noted that cetuximab and panitumumab were clinically equivalent ([Public Summary Document from the March 2015 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2015-03/panitumumab-vectibix-psd-03-2015)). An analysis of first initiators in 2016 showed that there was a higher proportional use of cetuximab (18%) compared to panitumumab (6%) for first-line therapy (Table 4).This likely reflects that cetuximab had more time to become established in the market due to its longer period of listing compared to panitumumab.

## Time on therapy

For patients first initiating on a targeted agent in 2014, the median time on all episodes of treatment was 517 days (around 17 months) (Table 5).

The time on any first-line targeted therapy compared with bevacizumab was similar (median 409 vs 427 days, respectively) as bevacizumab accounted for the majority of use (88%) in first-line (Figure 3). Based on the results of the AVF2107g, AVF2192g and AVF0780g trials presented in the [March 2008 PBAC submission for bevacizumab](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-03/pbac-psd-bevacizumab-mar08), the mean progression-free survival (PFS) time for bevacizumab in combination with either with 5-FU/LV or irinotecan plus 5-FU/LV for previously untreated mCRC patients was around 11 months (341 days). For the more commonly used chemotherapy partner identified in the analysis, XELOX, similar PFS times are reported in the literature (e.g. Antonuzzo et al., 2015; Matsui et al., 2016). Based on the FIRE-3 trial, the PFS for cetuximab in combination with FOLFIRI was 10.4 months with an upper confidence limit of 12.2 months (around 378 days), ([Public Summary Document for the cetuximab November 2014 submission](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-11/cetuximab-psd-11-2014)). The median time on any first-line targeted therapy or bevacizumab alone appeared to be longer than the PFS following first-line targeted therapy observed in clinical trials. This suggests that there may have been some use of the targeted drugs after disease progression which is not permitted under their restrictions. Investigations on the use of bevacizumab beyond disease progression have reported incremental benefits for overall survival (Cartwright et al., 2012; Bennouna et al., 2013) which may encourage this practice. For the trials considered in the March 2008 submission, the investigators assessed tumour responses and disease progression using the Response Evaluation Criteria in Solid Tumours (e.g. Hurwitz et al., 2005). The PBS restrictions for targeted therapy do not specify a particular assessment criterion to determine if a patient has progressive disease.

The time on second-line targeted therapy (median 129 days, Table 5), which mainly comprised of cetuximab (71%, Table 5), was similar to PFS data previously considered by PBAC for second-line cetuximab therapy. The November 2008 submission for cetuximab reported the PFS results from the BOND trial (Cunningham et al., 2004) where irinotecan refractory patients had a PFS of 4.1 months (around 127 days) when treated with cetuximab plus irinotecan in second line ([Public Summary Document for the cetuximab November 2008 submission](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-11/pbac-psd-cetuximab-nov08)).

# DUSC consideration

Colorectal cancer is the second most common cause of cancer death in Australia after lung cancer. The growth in the number of patients treated with bevacizumab, cetuximab and panitumumab began to slow in 2013 and had reached a plateau in 2016. DUSC noted the suggestion in the utilisation report that the declining growth in the use of the targeted therapies may reflect that some PBS eligible patients were participating in clinical trials instead of seeking PBS subsidised therapy. DUSC did not consider that this was a major factor noting that most of the current trials being conducted in Australia were for third-line therapy. DUSC also did not consider that the National Bowel Cancer Screening Program would have an impact on the number of patients with mCRC presenting for PBS subsidised therapy. DUSC noted that this program primarily detected patients in early stage disease and considered that patients with mCRC would be diagnosed early outside of this program.

DUSC noted that most patients were initiated on bevacizumab. DUSC considered that there may have been a preference for bevacizumab as side effects from this therapy were less common. DUSC noted that the development of acneiform skin rash was common in patients treated with cetuximab or panitumumab. The utilisation of cetuximab and panitumumab may have been lower relative to bevacizumab due to the impact of these therapies on a patient’s physical appearance.

DUSC noted that cetuximab had a greater market share compared to panitumumab. DUSC considered that this was likely to be due to cetuximab entering the market earlier than panitumumab rather than differences in the side effect profiles between the drugs. DUSC noted that panitumumab was fully humanised and may have less infusion related adverse events compared with cetuximab.

DUSC noted that there were differences in the response to treatment with regard to whether the tumour location is left-sided or right-sided in patients with mCRC. This relates to differing mutational profiles between each side with right-sided cancer generally having worse outcomes. DUSC noted that left-sided mCRC occurs in around two-thirds of patients. DUSC noted that left-sided mCRC favoured cetuximab in first-line[[11]](#footnote-11). DUSC considered that the increase in the utilisation of cetuximab in first-line from 2016 Quarter 2 could relate to the introduction of recommendations in clinical guidelines of its use to treat left-sided mCRC. DUSC commented that the choice of therapy may change in the future with further evidence around the impact of tumour sidedness on response to therapy.

Subsidised bevacizumab must be used in combination with chemotherapy. DUSC noted that there were very few cases where bevacizumab was potentially supplied as monotherapy.

DUSC noted that the median time on bevacizumab (14 months) was longer than the progression-free survival time observed in clinical trials. Disease progression in the trials was evaluated using the RECIST (Response Evaluation Criteria In Solid Tumors) criteria whereas the PBS restriction for bevacizumab does not specify any criteria to determine if a patient has progressive disease. DUSC considered that this may indicate that there was some use of bevacizumab beyond disease progression and that this may be driven by its more favourable toxicity profile. DUSC noted that there was evidence (e.g. Bennouna et al., 2013)[[12]](#footnote-12) of overall survival benefits from the use of bevacizumab beyond progression however this use is not TGA approved or PBS subsidised.

DUSC noted the results from the time to re-supply analysis for the targeted therapies. DUSC considered that the pattern of re-supply times were consistent with recommendations except for cetuximab. The Product Information recommends that cetuximab is administered once a week for all indications. DUSC noted that a relatively high proportion of patients were dispensed a further supply of cetuximab between 13 to 15 days. DUSC noted that there was trial evidence[[13]](#footnote-13) showing that cetuximab administered on an every-other-week (q2w) dosing schedule was comparable to the results obtained from a weekly regimen. DUSC considered that a q2w schedule would be preferred by patients and would decrease compounding and administration costs. DUSC considered that there were possible financial incentives for private providers to administer cetuximab as a weekly regimen.

Based on patients first initiating on targeted therapy in 2014 or 2016, the main chemotherapy partners used in combination with the targeted therapies were XELOX and FU-LV. The data analyses indicated that there was minimal use of irinotecan based therapies, including XELIRI and FOLFIRI. The data for the 2016 cohort were too premature to fully examine use in later lines of therapy. DUSC considered that the drug sequence results for the 2014 initiating cohort were surprising. The patterns of treatment identified from the analysis were inconsistent with the Committee’s understanding of current practice. Anomalies noted in the results included:

* a potential underrepresentation of irinotecan-based regimens; and
* XELOX was detected as being used in later lines of therapy. In this setting, it would be more common for capecitabine to be used as monotherapy or in combination with irinotecan-based chemotherapy.

DUSC noted the difficulties in attempting to identify the supply of chemotherapy regimens using PBS claims data. DUSC noted that the sequence of therapy by stage of disease may not be readily identified as some of the restrictions for chemotherapy drugs do not define the line of therapy or when treatment is given during disease progression. DUSC commented that it is usual practice that when chemotherapy regimens are de-intensified this occurs in the same line of therapy. This will be difficult to detect using PBS data alone. The approach used in the analysis was to set a “window” of time to detect chemotherapy medicines which may have been co-administered as part of a regimen. Except for folinic acid and leucovorin, a drug was assumed to be co-administered with another drug if its date of supply was within 42 days (i.e. median time to re-supply of 14 days multiplied by three) of the previous or next supply. The co-administration of folinic acid with other drugs was assumed if its supply occurred within 186 days (i.e. median time to re-supply of folinic acid of 62 days multiplied by three) before or after the date of supply of another drug. DUSC noted that oxaliplatin, irinotecan and capecitabine are unrestricted listings and that the use of these medicines for a particular stage of disease cannot be readily determined. DUSC commented that surplus medicines could potentially be used to make up a chemotherapy regimen and therefore some components of the regimen may not be dispensed at the time of other components.

DUSC noted that there was a need to improve the ability to identify the use of drug regimens within claims data to better understand the utilisation of PBS subsidised chemotherapy. DUSC requested that further work be done out-of-session to investigate the development of improved methods to undertake analyses on the use of chemotherapy regimens. DUSC recommended that pharmacists should be consulted to ensure that the methods account for particular dispensing practices which may influence the detection of co-administered drugs. DUSC considered that confirming medicine discontinuation due to death prior to undertaking an analysis of regimen use may lead to more robust results. DUSC noted that death data cannot be readily obtained for incorporation into DUSC reporting. DUSC requested that its Secretariat follow-up on the availability and process to request death data. DUSC considered this may also be beneficial for duration of therapy analyses and for reviewing utilisation in therapeutic areas other than cancer medicines. DUSC suggested that consideration should also be given to the use of a proxy for actual death data.

# DUSC actions

* DUSC requested that the report be provided to the PBAC.
* DUSC requested the DUSC Secretariat investigate options for the development of analytical techniques to improve the detection of chemotherapy regimens within the PBS claims data.
* DUSC suggested that the analysis of chemotherapy regimens be removed from the report before publication.

# Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

# Sponsors’ comments

The sponsors had no comment.

# Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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# Appendix 1: PBS listings for bevacizumab, cetuximab and panitumumab as at 1 October 2017

**Table A1.1: PBS listings of bevacizumab, cetuximab and panitumumab**

| Item | Name, form & strength, pack size | Max. amount | Rpts | DPMA1 | Brand name and manufacturer |
| --- | --- | --- | --- | --- | --- |
| 4400N | Bevacizumab, Solution for I.V. infusion 100 mg in 4 mL | 900 mg | 11 | $3760.33 | Avastin, Roche Products Pty Ltd |
|  | Bevacizumab, Solution for I.V. infusion 400 mg in 16 mL |  |  |  |  |
| 7243F | Bevacizumab, Solution for I.V. infusion 100 mg in 4 mL | 900 mg | 11 | $3850.45 | Avastin, Roche Products Pty Ltd |
|  | Bevacizumab, Solution for I.V. infusion 400 mg in 16 mL |  |  |  |  |
| 4436L  (Initial) | Cetuximab, Solution for I.V. infusion 100 mg in 20 mL | 880 mg | 0 | $2999.38 | Erbitux, Merck Serono Australia Pty Ltd |
|  | Cetuximab, Solution for I.V. infusion 500 mg in 100 mL |  |  |  |  |
| 4731B  (Continuing) | Cetuximab, Solution for I.V. infusion 100 mg in 20 mL | 550 mg | 11 | $2027.53 | Erbitux, Merck Serono Australia Pty Ltd |
|  | Cetuximab, Solution for I.V. infusion 500 mg in 100 mL |  |  |  |  |
| 7242E  (Initial) | Cetuximab, Solution for I.V. infusion 100 mg in 20 mL | 880 mg | 0 | $3078.86 | Erbitux, Merck Serono Australia Pty Ltd |
|  | Cetuximab, Solution for I.V. infusion 500 mg in 100 mL |  |  |  |  |
| 7273T  (Continuing) | Cetuximab, Solution for I.V. infusion 100 mg in 20 mL | 550 mg | 11 | $2093.39 | Erbitux, Merck Serono Australia Pty Ltd |
|  | Cetuximab, Solution for I.V. infusion 500 mg in 100 mL |  |  |  |  |
| 10262D  (Continuing) | Cetuximab, Solution for I.V. infusion 100 mg in 20 mL | 550 mg | 18 | $2027.53 | Erbitux, Merck Serono Australia Pty Ltd |
|  | Cetuximab, Solution for I.V. infusion 500 mg in 100 mL |  |  |  |  |
| 10265G  (Continuing) | Cetuximab, Solution for I.V. infusion 100 mg in 20 mL | 550 mg | 18 | $2093.39 | Erbitux, Merck Serono Australia Pty Ltd |
|  | Cetuximab, Solution for I.V. infusion 500 mg in 100 mL |  |  |  |  |
| 10069Y  (Private hospital, Initial and continuing) | Panitumumab, Solution concentrate for I.V. infusion 100 mg in 5 mL | 720 mg | 5 | $6027.99 | Vectibix, Amgen Australia Pty Limited |
|  | Panitumumab, Solution concentrate for I.V. infusion 400 mg in 20 mL |  |  |  |  |
| 10082P  (Public hospital, Initial and continuing) | Panitumumab, Solution concentrate for I.V. infusion 100 mg in 5 mL | 720 mg | 5 | $5907.83 | Vectibix, Amgen Australia Pty Limited |
|  | Panitumumab, Solution concentrate for I.V. infusion 400 mg in 20 mL |  |  |  |  |
| 10508C  (Private hospital, Initial and continuing) | Panitumumab, Solution concentrate for I.V. infusion 100 mg in 5 mL | 720 mg | 9 | $6027.99 | Vectibix, Amgen Australia Pty Limited |
|  | Panitumumab, Solution concentrate for I.V. infusion 400 mg in 20 mL |  |  |  |  |
| 10513H  (Public hospital, Initial and continuing) | Panitumumab, Solution concentrate for I.V. infusion 100 mg in 5 mL | 720 mg | 9 | $5907.83 | Vectibix, Amgen Australia Pty Limited |
|  | Panitumumab, Solution concentrate for I.V. infusion 400 mg in 20 mL |  |  |  |  |

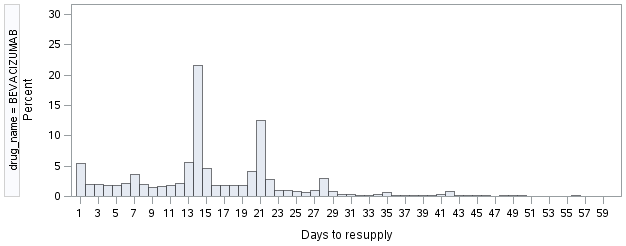
Source: the [PBS website](http://www.pbs.gov.au/pbs/home). Special pricing arrangements apply for the listings of bevacizumab, cetuximab and panitumumab.

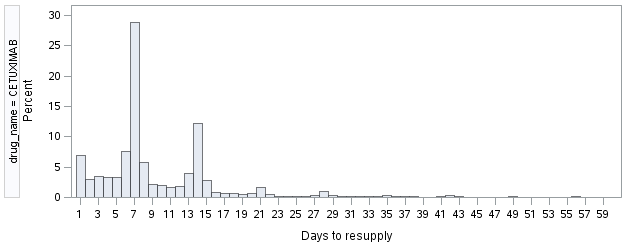
1DPMA = The Dispensed Price for Maximum Amount (DPMA) is given for Efficient Funding of Chemotherapy injectables.

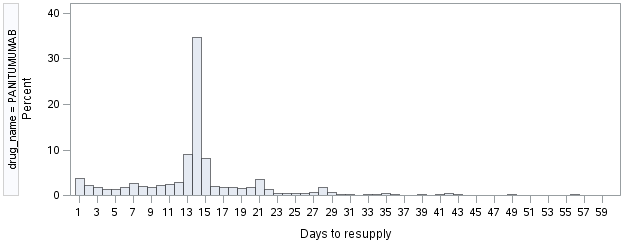
# Appendix 2: Analyses of the time to resupply

To identify the co-administration of drugs, it was assumed that two or more drugs were co-administered if they were supplied within 42 days of the given date of dispensing for each drug. This was derived from the median of 14 coverage days across all drugs multiplied by three to allow for potential breaks in therapy. To examine whether 42 days allowed sufficient time to detect co-administration, the distributions of the time to resupply for each drug was examined.

For all drugs included in the co-administration analysis, 98% of prescriptions were dispensed within 42 days of the previous supply of the drug (see Figures A2.1 and A2.2).

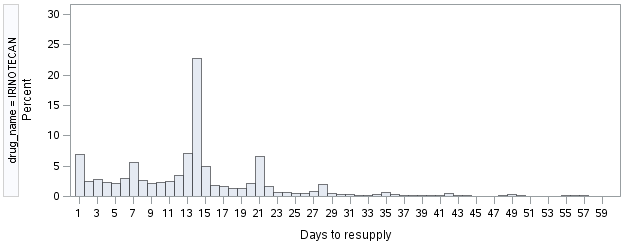


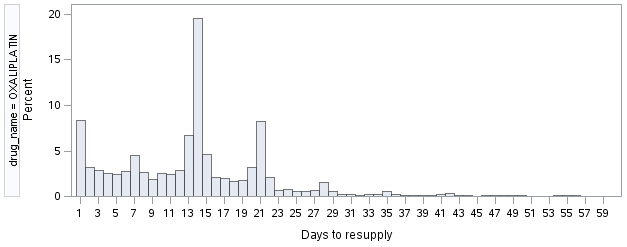


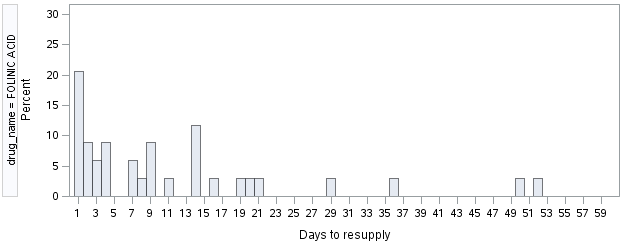


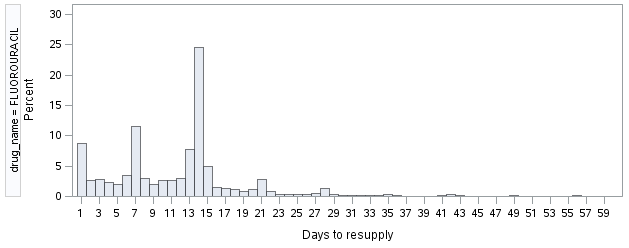
**Figure A2.1. Time to resupply for bevacizumab, cetuximab and panitumumab**

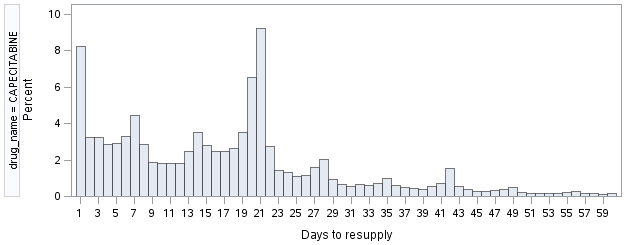
The distribution of the resupply times for bevacizumab, cetuximab and bevacizumab were consistent with the recommended dosing regimens. Bevacizumab is administered every 2 or 3 weeks depending on the body weight of the patient. It was generally resupplied on days 14 and 21 (Figure A2.1). The pattern of resupply times for cetuximab was consistent with its recommended once weekly administrations (Figure A.1). Panitumumab is administered every two weeks and the majority of its resupply occurred on day 14 (Figure A2.1).











**Figure A2.2. Time to resupply for irinotecan, oxaliplatin, folinic acid and fluorouracil**

# Appendix 3: Number of infusions

## Number of infusions

The number of prescriptions for infusible chemotherapy medicines was influenced by the introduction of the Revised Arrangements for the Efficient Funding of Chemotherapy Drugs (referred to here as the ‘EFC’). Under these arrangements, prescribers submit dose specific prescriptions in milligrams rather than the former arrangements where prescriptions were written for specific forms and strengths of a medicine. Also, suppliers are reimbursed for the most cost efficient combination of vials to make up the required dose. The EFC was introduced for community pharmacies and private hospitals on 1 December 2011 and for public hospital pharmacies by 1 April 2012. To account for the introduction of the EFC arrangements, the number of infusions was examined for bevacizumab, cetuximab and panitumumab. Refer to the ‘Methods’ section for the approach that was used to convert individual vial prescriptions to infusions.

The number of infusions for bevacizumab had remained relatively stable since May 2013 (Figure A3.1). A negative trend in the number of infusions for cetuximab occurred from April 2014 which coincided with the first listing of panitumumab (Figure A3.2). The subsequent increase in the number of infusions for cetuximab from mid-2015 was likely from its listing as a first-line treatment from 1 June 2015 (Figure A3.2).

The number of infusions for panitumumab had continued to increase since its first listing in April 2014 (Table A3.1, Figure A3.3).

**Table A3.1. Number of infusions for bevacizumab, cetuximab and panitumumab by line of therapy and by year**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **2009 (YTD)a** | **2010** | **2011** | **2012** | **2013** | **2014** | **2015** | **2016** | **2017 (YTD)b** |
| **BEVACIZUMAB**  ***Subtotal – all lines*** | ***5,767*** | ***21,147*** | ***24,762*** | ***27,275*** | ***31,023*** | ***31,903*** | ***32,681*** | ***32,659*** | ***18,180*** |
| 1: First-line | 5,767 | 21,147 | 24,745 | 27,101 | 30,862 | 31,737 | 32,349 | 31,715 | 17,337 |
| 2: Second-line |  |  |  | 53 | 26 | 22 | 122 | 573 | 613 |
| 3: After second-line |  |  | 17 | 121 | 135 | 144 | 210 | 371 | 230 |
| **CETUXIMAB**  ***Subtotal – all lines*** |  |  | ***2,958*** | ***14,808*** | ***15,935*** | ***15,269*** | ***13,536*** | ***14,929*** | ***7,692*** |
| 1: First-line |  |  | 1,150 | 5,255 | 4,832 | 4,486 | 4,369 | 6,925 | 3,836 |
| 2: Second-line |  |  | 1,786 | 9,337 | 10,888 | 10,594 | 8,810 | 7,563 | 3,618 |
| 3: After second-line |  |  | 22 | 216 | 215 | 189 | 357 | 441 | 238 |
| **PANITUMUMAB**  ***Subtotal – all lines*** |  |  |  |  |  | ***783*** | ***2,186*** | ***3,529*** | ***2,876*** |
| 1: First-line |  |  |  |  |  | 210 | 637 | 1,307 | 1,188 |
| 2: Second-line |  |  |  |  |  | 452 | 1,294 | 1,910 | 1,449 |
| 3: After second-line |  |  |  |  |  | 121 | 255 | 312 | 239 |
| **Total infusions for all drugs** | **5,767** | **21,147** | **27,720** | **42,083** | **46,958** | **47,955** | **48,403** | **51,117** | **28,748** |

Note:

a Part-year data from 1 July 2009 (i.e. first listing date for bevacizumab) to 31 December 2009.

b Part-year data from 1 January 2017 to 31 July 2017.

Bevacizumab

**Figure A3.1. Number of infusions for bevacizumab**

## Cetuximab

**Figure A3.2. Number of infusions for cetuximab**

## Panitumumab

**Figure A3.3. Number of infusions for panitumumab**

1. Cancer Australia. Bowel cancer statistics. Accessed on 17 October 2017 at: https://bowel-cancer.canceraustralia.gov.au/statistics [↑](#footnote-ref-1)
2. Riihimäki, M. et al. Patterns of metastasis in colon and rectal cancer. Sci. Rep. 6, 29765; doi: 10.1038/srep29765 (2016). [↑](#footnote-ref-2)
3. Bowel Cancer Australia. Accessed on 22 November 2017 at: https://www.bowelcanceraustralia.org/5-year-survival. [↑](#footnote-ref-3)
4. FOLFOX = folinic acid + fluorouracil + oxaliplatin. [↑](#footnote-ref-4)
5. FOLFIRI = irinotecan + fluorouracil + folinic acid. [↑](#footnote-ref-5)
6. Full implementation of the program is expected by 2020. Under this program, eligible Australians are sent screening tests via mail which can be completed without cost. Source: Bowel Cancer Australia. Accessed on 20 November 2017 at: http://www.bowelscreenaustralia.org/ [↑](#footnote-ref-6)
7. BEACON CRC. Study of Encorafenib + Cetuximab Plus or Minus Binimetinib vs. Irinotecan/Cetuximab or Infusional 5-Fluorouracil (5-FU)/Folinic Acid (FA)/Irinotecan (FOLFIRI)/Cetuximab With a Safety Lead-in of Encorafenib + Binimetinib + Cetuximab in Patients With BRAF V600E-mutantMetastatic Colorectal Cancer. ClinTrials.gov Identifier: NCT02928224. Accessed on 20 November 2017 at: https://clinicaltrials.gov [↑](#footnote-ref-7)
8. ElevatION: CRC-101: A Phase Ib Study of PDR001 in Combination With Bevacizumab and mFOLFOX6 as First Line Therapy in Patients With Metastatic MSS Colorectal Cancer. ClinTrials.gov Identifier: NCT03176264. Accessed on 20 November 2017 at: https://clinicaltrials.gov [↑](#footnote-ref-8)
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10. Grothey, A. and Clark, J.W. (2017) Patient education: Colorectal cancer treatment; metastatic cancer (Beyond the Basics). Accessed on 30 November 2017 at: https://www.uptodate.com [↑](#footnote-ref-10)
11. Tejpar, S., Stintzing, S., Ciardiello, F. et al. Prognostic and Predictive Relevance of Primary Tumor Location in Patients With RAS Wild-Type Metastatic Colorectal Cancer Retrospective Analyses of the CRYSTALand FIRE-3 Trials. JAMA Oncol. doi:10.1001/jamaoncol.2016.3797. [↑](#footnote-ref-11)
12. Bennouna J, Sastre J, Arnold D, Österlund P, Greil R, Van Cutsem E, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial, Lancet Oncol 2013; 14(1): 29-37. Doi: 10.1016/S1470-2045(12)70477-1. [↑](#footnote-ref-12)
13. # Hubbard, J.M and Alberts, S.J. (2013) Alternate dosing of cetuximab for patients with metastatic colorectal cancer. [Gastrointest Cancer Res.](https://www.ncbi.nlm.nih.gov/pubmed/23745159) 2013 Mar;6(2):47-55.

    [↑](#footnote-ref-13)