

Analysis of medicines for the treatment of locally advanced and metastatic breast cancer: including a 24 month predicted versus actual analysis of palbociclib

Drug utilisation sub-committee (DUSC)

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Abstract

Purpose

To review the utilisation of medicines for locally advanced and metastatic breast cancer (BC) treatments including a predicted versus actual analysis of palbociclib in the first 24 months of R/PBS listing.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Palbociclib was first listed on the PBS on 1 May 2019.

Data Source / methodology

Data extracted from the PBS data maintained by Department of Health, processed by Services Australia was used for the analyses.

Key Findings

- The utilisation of palbociclib has been greater than predicted. The number of patients supplied palbociclib was 1,540 in Year 1 and 2,261 in Year 2. Of all BC listings, palbociclib had the highest PBS expenditure by 2021 Q3 based on the published list price.
- As at 2021 Q3, there were around 93,000 patients supplied a PBS listing for BC.
- The number of initiating patients on BC listings has remained relatively stable at around 7,500 patients per quarter since 2019 Q3.
- Letrozole, anastrozole and tamoxifen had the highest utilisation to treat hormone receptor positive BC, the most common subtype of breast cancers. Government expenditure on hormone modulating BC treatments, including letrozole, anastrozole, tamoxifen, exemestane and fulvestrant, has significantly reduced over time due to several price reductions have been applied to these listings.

Purpose of analysis

To review the utilisation of medicines for locally advanced and metastatic breast cancer (BC) treatments including a predicted versus actual analysis of palbociclib in the first 24 months of R/PBS listing.

Background

Clinical situation

BC is the most common cancer in women in Australia (apart from non-melanoma skin cancer) and the second most common cancer to cause death in women, after lung cancer.

BC is the abnormal growth of the cells lining the breast lobules or ducts. These cells grow uncontrollably and have the potential to spread to other parts of the body. All genders can develop BC however it is more common in women than men, transwomen, or non-binary people. Breast cancer in men is rare (less than 1 percent of all breast cancers). Transgender people taking oestrogen however may have an increased risk of developing breast cancer.

It is estimated that 19,866 women and 164 men in Australia will be diagnosed with BC in 2021.¹

In Australia, the overall five year survival rate for BC in females is 91%. If the cancer is limited to the breast, 96% of patients will be alive five years after diagnosis; this figure excludes those who die from other diseases. If the cancer has spread to the regional lymph nodes, five year relative survival drops to 80%.¹

BC invades locally and spreads through the regional lymph nodes, bloodstream, or both. Metastatic breast cancer may affect almost any organ in the body—most commonly, lungs, liver, bone, brain, and skin. Most skin metastases occur near the site of breast surgery; scalp metastases are uncommon.

Some BCs may recur sooner than others; recurrence can often be predicted based on tumour markers. For example, metastatic breast cancer may occur within three years in patients who are negative for tumour markers or occur > 10 years after initial diagnosis and treatment in patients who have an estrogen-receptor positive tumour.

Estrogen and progesterone receptors, present in some BC, are nuclear hormone receptors that promote DNA replication and cell division when the appropriate hormones bind to them. Thus, drugs that block these receptors may be useful in treating tumours with the receptors. About two thirds of postmenopausal patients with cancer have

¹ Cancer Council. Breast cancer: Causes, Symptoms and Treatments, Available from: <https://www.cancer.org.au/cancer-information/types-of-cancer/breast-cancer>

an estrogen receptor–positive (ER+) tumour. Incidence of ER+ tumours is lower among premenopausal patients.

Another cellular receptor is human epidermal growth factor receptor 2 (HER2; also called HER2/neu or ErbB2); its presence correlates with a poorer prognosis at any given stage of cancer. In about 20% of patients with BC, HER2 receptors are overexpressed. Drugs that block these receptors are part of standard treatment for these patients.²

Treatment for BC depends on the extent of the cancer, and usually includes surgical excision, often with radiation therapy, with or without adjuvant chemotherapy, hormone therapy, or both.

Chemotherapy is often used in the following scenarios:

- Neoadjuvant – to shrink tumours and allow for surgery or other treatments
- Adjuvant – To reduce the risk of recurrence of the cancer following surgery
- For the treatment of metastatic breast cancer

The following medicines were considered in this review and are used to treat BC or supplement regimens and include neoadjuvant, adjuvant and metastatic medicines: abemaciclib, anastrozole, eribulin, everolimus, exemestane, fulvestrant, lapatinib, letrozole, nanoparticle albumin-bound paclitaxel (NAB pac), palbociclib, peg-doxorubicin, pertuzumab, ribociclib, tamoxifen, trastuzumab, trastuzumab emtansine and vinorelbine.

This review examines these medicines from the first quarter of 2015, and includes a 24 month predicted versus actual analysis of palbociclib.

Palbociclib

Palbociclib is used in the treatment of inoperable locally advanced or metastatic hormone receptor positive BC. Palbociclib inhibits two proteins which drive the growth of tumour cells.

Palbociclib is a protein kinase inhibitor PBS subsidised for inoperable locally advanced or metastatic breast cancers (MBC) that are hormone receptor positive, HER2 negative and must be used in combination with an aromatase inhibitor.

The Herceptin Program

The Herceptin Program was implemented from 1 December 2001 by the government to provide access to trastuzumab 150 mg vials for treatment of HER2 expressing (HER2+) MBC. This program was managed separately to the PBS.

The Herceptin Program concluded in the second quarter of 2015. A subset of the graphs and tables in this report include data which covers the first quarter of 2015, when the Herceptin Program was still in place.

² Kosir M.A, Breast Cancer-Gynecology and Obstetrics- MSD Manual Professional Edition (2020). Available from: <https://www.msdmanuals.com/en-au/professional/gynecology-and-obstetrics/breast-disorders/breast-cancer>

Pharmacology

Palbociclib is a cyclin-dependent kinase (CDK) inhibitor which prevents the activation of CDK 4 and 6. Cyclin D1 and CDK4/6 are downstream of multiple signalling pathways which lead to cellular proliferation and their activity is increased in hormone-receptor-positive breast cancers.³

When used as initial therapy, palbociclib should be given in combination with an aromatase inhibitor such as letrozole. However, in women who have progressed on previous endocrine-based therapy, it can be given with the oestrogen receptor antagonist fulvestrant noting that this is not PBS subsidised.⁴

Therapeutic Goods Administration (TGA) approved indications

Palbociclib was TGA registered on 3 May 2017 for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic BC in combination with:

- an aromatase inhibitor as initial endocrine-based therapy;
- fulvestrant in patients who have progressed on previous endocrine-based therapy.

Dosage and administration

Table 1: Dosage and administration of palbociclib

Brand name and sponsor	Product	Dose and frequency of administration
Ibrance, Pfizer Australia Pty Ltd	Palbociclib capsule 75mg, 100mg and 125mg	Daily for 3 weeks followed by a 1 week break

Source: TGA Product Information

Dosage

The recommended dose of palbociclib is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Treatment should continue until disease progression. When co-administered with palbociclib, an aromatase inhibitor should be administered according to the dose schedule reported in the Product Information for that aromatase inhibitor. When co-administered with palbociclib, the recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, 29 and once monthly thereafter. Please refer to the Product Information for fulvestrant for further details.

³ Ibrance (palbociclib). Australian Approved Product Information. Sydney: Pfizer Australia Pty Ltd. Approved 3 May 2017, updated 3 June 2020. Available from < <https://www.tga.gov.au/product-information-pi>.>

⁴ Palbociclib for breast cancer. Australian Prescriber (2018). 41: 127-8. <https://doi.org/10.18773/austprescr.2018.029>

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA \(Product Information\)](#) and [the TGA \(Consumer Medicines Information\)](#).

PBS listing details (as at December 2021)

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended the listing of palbociclib in combination with a nonsteroidal aromatase inhibitor (NSAI) (anastrozole or letrozole) as initial endocrine based therapy in patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced inoperable or metastatic BC at the March 2018 PBAC meeting.⁵

Palbociclib was first listed on the PBS from 1 May 2019.

Table 2: PBS listing of palbociclib

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
11698Q	Palbociclib 125mg capsule	1	5	\$4,249.07	Ibrance Pfizer Australia Pty Ltd
11700T	Palbociclib 100mg capsule	1	5	\$4,249.07	Ibrance Pfizer Australia Pty Ltd
11699R	Palbociclib 75 mg capsule	1	5	\$4,249.07	Ibrance Pfizer Australia Pty Ltd

Source: the [PBS website](#).

Restriction

Locally advanced or metastatic breast cancer

Authority Required

Treatment Phase: Initial treatment

Clinical criteria:

- Patient must not have previously been treated with an aromatase inhibitor for advanced or metastatic breast cancer,

AND

- Patient must not have previously been treated with abemaciclib or ribociclib; OR
- Patient must have developed an intolerance to abemaciclib or ribociclib of a severity necessitating permanent treatment withdrawal,

AND

⁵ Palbociclib, Public Summary Document, March 2018 PBAC Meeting. Available from: <https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2018-03/Palbociclib-psd-march-2018>

- The condition must be hormone receptor positive,
AND
- The condition must be human epidermal growth factor receptor 2 (HER2) negative,
AND
- The condition must be inoperable,
AND
- Patient must have a World Health Organization (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less,
AND
- The treatment must be in combination with anastrozole or letrozole,
AND
- The treatment must not be in combination with abemaciclib or ribociclib.

Population criteria:

- Patient must not be premenopausal.

Authority Required

Locally advanced or metastatic breast cancer

Treatment Phase: Continuing treatment

Clinical criteria:

- Patient must have previously received PBS-subsidised treatment with this drug for this condition,

AND

- Patient must not develop disease progression while receiving treatment with this drug for this condition,

AND

- Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST),

AND

- The treatment must be in combination with anastrozole or letrozole,

AND

- The treatment must not be in combination with abemaciclib or ribociclib.

Population criteria:

- Patient must not be premenopausal.

A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.

For details of the current PBS listing refer to the [PBS website](#).

Changes to listing

PBS listing changes for Palbociclib

Date	Action	Change
1 May 2019	Palbociclib listed on PBS	The treatment must not be in combination with ribociclib.
1 January 2020	Change to listing	The treatment must not be in combination with abemaciclib or ribociclib.
1 October 2020	Change to listing	Grandfather restriction removed.

PBS streamlining of breast cancer drugs in this review from January 2015

Drug	Date of listing	Date of change	Action
Eribulin	31 December 2014	30 June 2016	Streamlined
Trastuzumab	31 December 2006	31 October 2019	Streamlined
Fulvestrant	1 April 2021	30 June 2021	Streamlined
Lapatinib	1 May 2008	1 October 2019	Continuing prescriptions streamlined

Current PBS listing details are available from the [PBS website](#).

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

The PBAC considered and did not recommend palbociclib at the March 2017 and November 2017 meetings.

At the March 2018 meeting the PBAC recommended the listing of palbociclib in combination with a non-steroidal aromatase inhibitor (NSAI) (anastrozole or letrozole) as initial endocrine-based therapy in patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced inoperable or metastatic BC. The PBAC was satisfied that for some patients, palbociclib provided additional progression free survival compared with an NSAI alone, though its effect on overall survival was uncertain.⁶

The key differences between the March 2018 and the 2017 resubmissions were:

- A further price reduction was proposed.
- Alternative approaches to the calculation of treatment costs in the economic model were presented.
- A risk-share agreement was proposed.

PBAC noted that palbociclib should be treated as interchangeable on an individual patient basis with ribociclib and that palbociclib is not suitable for prescribing by nurse practitioners.

⁶ <https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2018-03/Palbociclib-psd-march-2018>

For further details refer to the [Public Summary Document](#) from the March 2018 PBAC meeting.

Previous reviews by the DUSC

For details of the DUSC consideration of trastuzumab, trastuzumab emtansine (T-DM1) and pertuzumab for the treatment of human epidermal growth factor receptor 2 (HER2) positive MBC refer to the [Public Release Document](#) from the February 2018 DUSC meeting.

For details of the DUSC consideration of a 24 month predicted versus actual review of everolimus for metastatic (Stage IV) BC refer to the [Public Release Document](#) from the February 2017 DUSC meeting.

Methods

Data was extracted from the Services Australia prescription database for all PBS items that had a BC restriction from 1 January 2015 until the end of September 2021 (based on date of supply). Of these PBS items there were several that also had other indications in addition to BC. For these items, prescriptions were classified as for treatment of BC or not, based on the Services Australia Authority approval database restriction code or the Streamlined Authority code in the prescription database.

Goserelin was the only “Restricted Benefit” medicine whose items had both BC and non-BC indications. As these PBS items do not require Streamlined, telephone or written authority approval, the supply for BC could not be determined. Thus goserelin was excluded from the analysis.

Patient Counts

Prevalent patients are the count of unique patient identifiers (IDs) on prescriptions for the analysis period (i.e. quarterly in the time series graphs and yearly in the Predicted vs Actual analysis). In this report, initiating patients were defined as patients who had not had a prescription for the drug / drug group since 1 January 2015. The patient counts start from 2016 Q1, so all initiators have at least 12 months with no prior supply.

As these analyses use date of supply prescription data, there may be small differences compared with publicly available Services Australia PBS date of processing data⁷ which only includes subsidised PBS and Repatriation PBS (R/PBS) prescriptions (i.e. prescriptions under the patient co-payment are not included). The Services Australia prescription database data used in this report includes under co-payment prescriptions from 1 April 2012.

Data Source / methodology

⁷ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <https://www.servicesaustralia.gov.au/organisations/about-us/reports-and-statistics/statistical-information-and-data-0/medicare-statistics/pharmaceutical-benefits-schedule-statistics>

Data were extracted from the Services Australia Supplied Prescription database for all PBS items that have a BC restriction. The Services Australia Authority Approvals database was used to determine the treatment indication when the PBS item code was not indication specific.

Results

Analysis of drug utilisation

Overall utilisation

Figures 1, 2, 3, 4 and 5 and Table 1 show the total supply of BC drugs that make up this review. These graphs and table show that the overall supply of BC medicines has increased at a consistent rate over the reporting period 2015 Q1 to 2021 Q3. However, when looking at single drugs, it is clear that letrozole, anastrozole and tamoxifen are the most commonly supplied drugs.

The medicines have been split into three categories; hormone modulating medicines (Figures 6a to 6f); protein kinase modulators (Figures 7a to 7f); and remaining medicines for BC including chemotherapy and immunotherapy (Figures 8a to 8f). The data for each of these categories are presented in the following six graphs:

- a) number of prescriptions supplied by drug
- b) total number of prescriptions supplied
- c) expenditure by drug (based on the published list prices)
- d) total expenditure (based on the published list prices)
- e) initiating patients
- f) prevalent patients

Note that the labels for doxorubicin hydrochloride (as pegylated liposomal) has been shortened to doxorubicin hydrochloride and nanoparticle albumin-bound paclitaxel has been shortened to NAB paclitaxel and that vinorelbine is the tablet formulation.

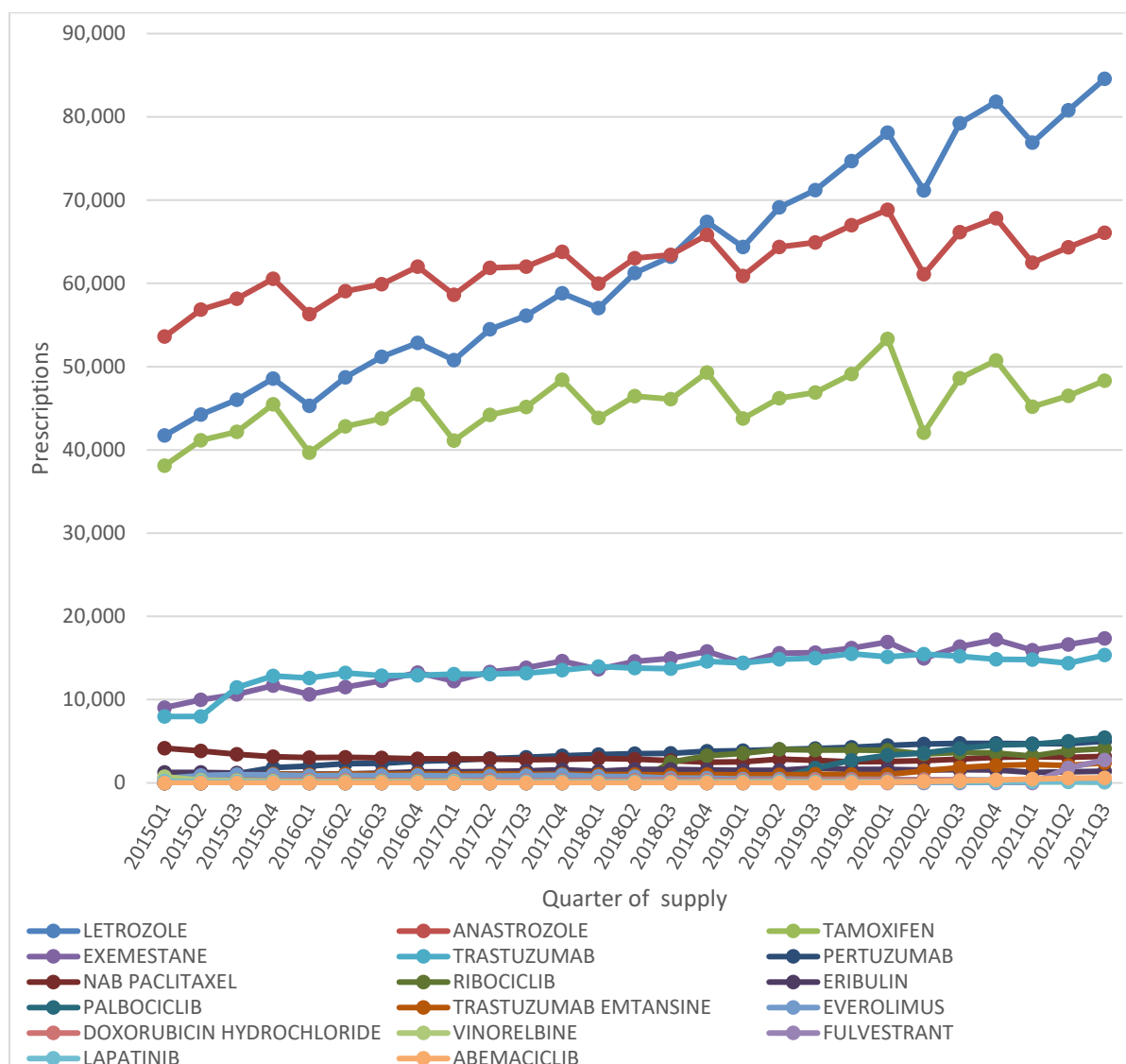


Figure 1a: Number of prescriptions supplied for breast cancer drugs by quarter

Source: Services Australia prescriptions database, extracted December 2021

Figure 1a shows that letrozole has the highest number of prescriptions dispensed, followed by anastrozole and tamoxifen.

This graph has been further split into three medicine group categories as described above (Figures 6a, 7a and 8a).

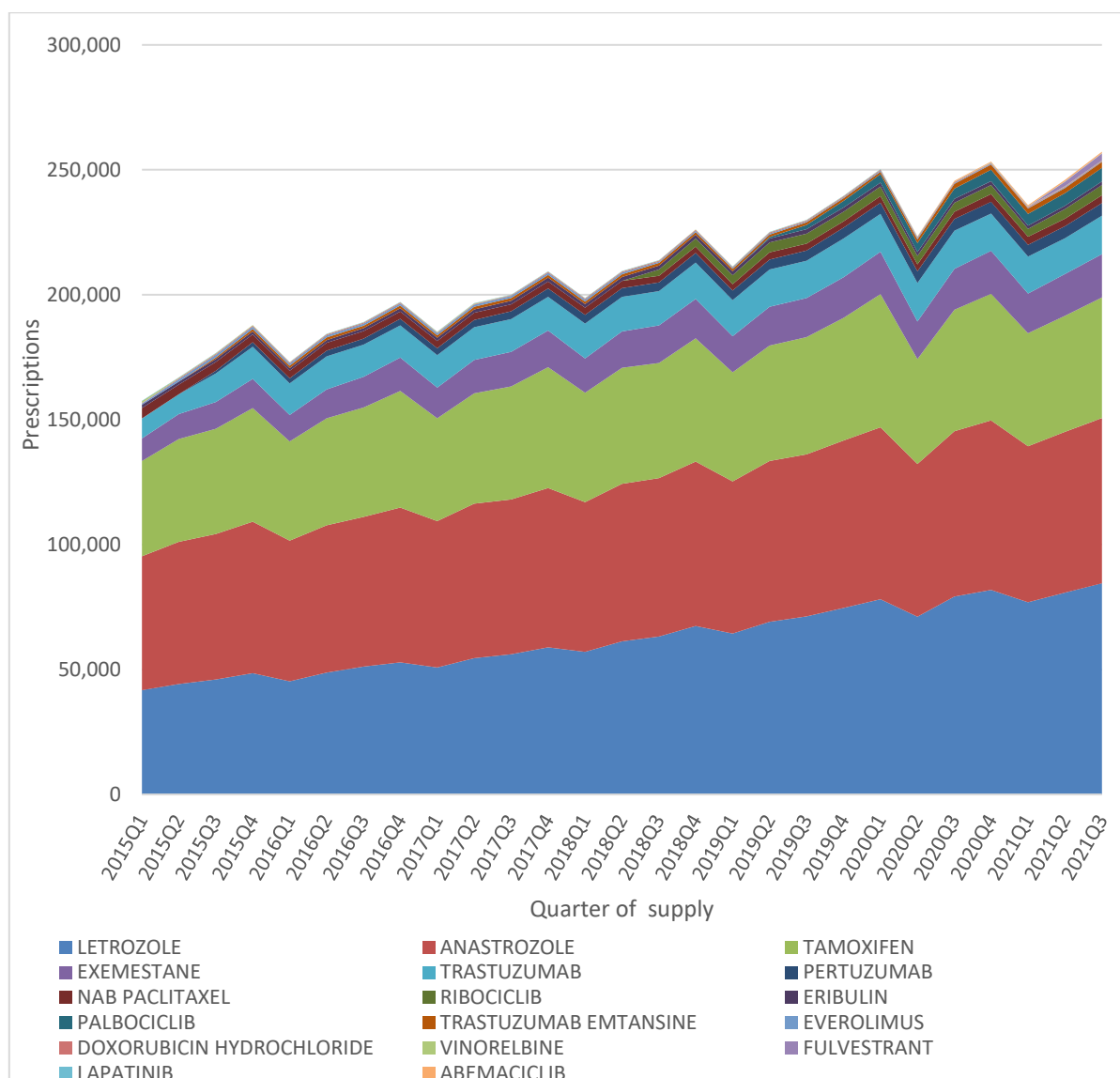


Figure 1b: Total number of prescriptions supplied for breast cancer drugs by quarter

Source: Services Australia prescriptions database, extracted December 2021

Figure 1b shows that the number of prescriptions dispensed for BC medicines has consistently increased each year since 2015, reaching a peak in supply in the second half of each year.

This graph has been further split into three medicine categories as described above (Figures 6b, 7b and 8b).

Table 1: Breast cancer drug prescriptions dispensed by drug by year

Prescription count								
Drug	2015	2016	2017	2018	2019	2020	2021*	Grand Total
LETROZOLE	180,593	198,049	220,218	248,881	279,358	310,337	242,259	1,679,695
ANASTROZOLE	229,181	237,271	246,312	252,236	257,156	263,921	192,906	1,678,983
TAMOXIFEN	166,896	172,955	178,929	185,718	185,965	194,732	140,021	1,225,216
EXEMESTANE	41,358	47,654	54,007	58,996	61,803	65,472	49,914	379,204
TRASTUZUMAB	40,297	51,657	52,884	56,128	59,761	60,692	44,557	365,976
PERTUZUMAB	2,950	9,316	11,992	14,275	16,308	18,664	14,431	87,936
NAB PACLITAXEL	14,629	12,022	11,335	10,983	10,641	11,182	9,391	80,183
RIBOCICLIB				5,741	15,446	14,610	11,210	47,007
ERIBULIN	4,794	4,662	5,718	6,210	6,488	6,326	4,034	38,232
PALBOCICLIB					5,063**	15,618	15,077	30,695
TRASTUZUMAB EMTANSINE	1,743	4,207	4,177	4,035	3,965	6,413	6,751	31,291
EVEROLIMUS	3,411	3,490	3,419	2,692	1,793	1,492	762	17,059
DOXORUBICIN HYDROCHLORIDE	1,120	1,239	1,153	1,278	1,373	1,319	817	8,299
VINORELBINE	1,591	687	585	535	526	511	345	4,780
FULVESTRANT							4552	4,552
LAPATINIB	553	319	445	447	451	439	342	2,996
ABEMACICLIB						862	1,627	2,489
Grand Total	689,116	743,528	791,174	848,155	901,034	972,590	738,996	5,684,593
Growth from previous year	-	7.90%	6.41%	6.72%%	6.23%%	7.94%	-	-

Source: Services Australia prescriptions database, extracted December 2021

*Data for 2021 is until September 2021.

** Palbociclib was listed on the PBS on 1 May 2019 so the data for 2019 is only for 7 months

The growth of BC prescriptions supplied has increased at a rate between 6.23% to 7.94% each year.

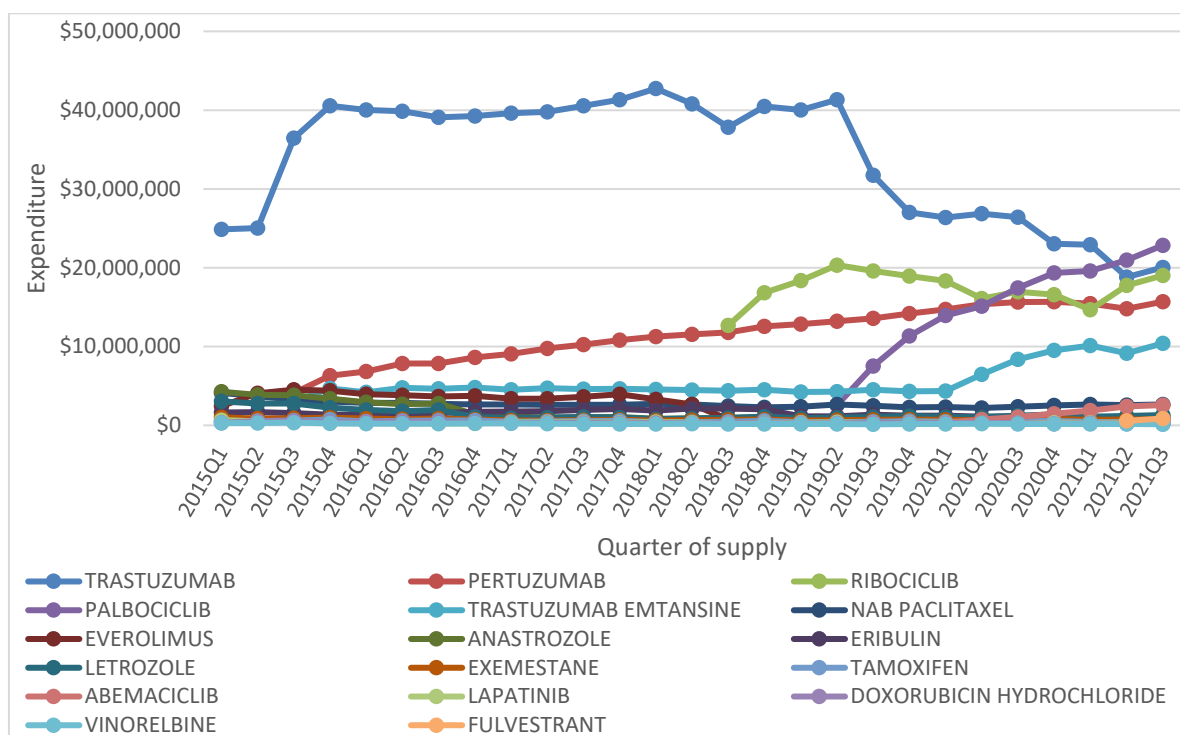


Figure 2a: Total Government expenditure on breast cancer drugs by quarter

Source: Services Australia prescriptions database, extracted December 2021

Note: All figures are based on published prices and are net of patient co-payments. Some medicines have special pricing arrangements and government expenditure may be less than presented.

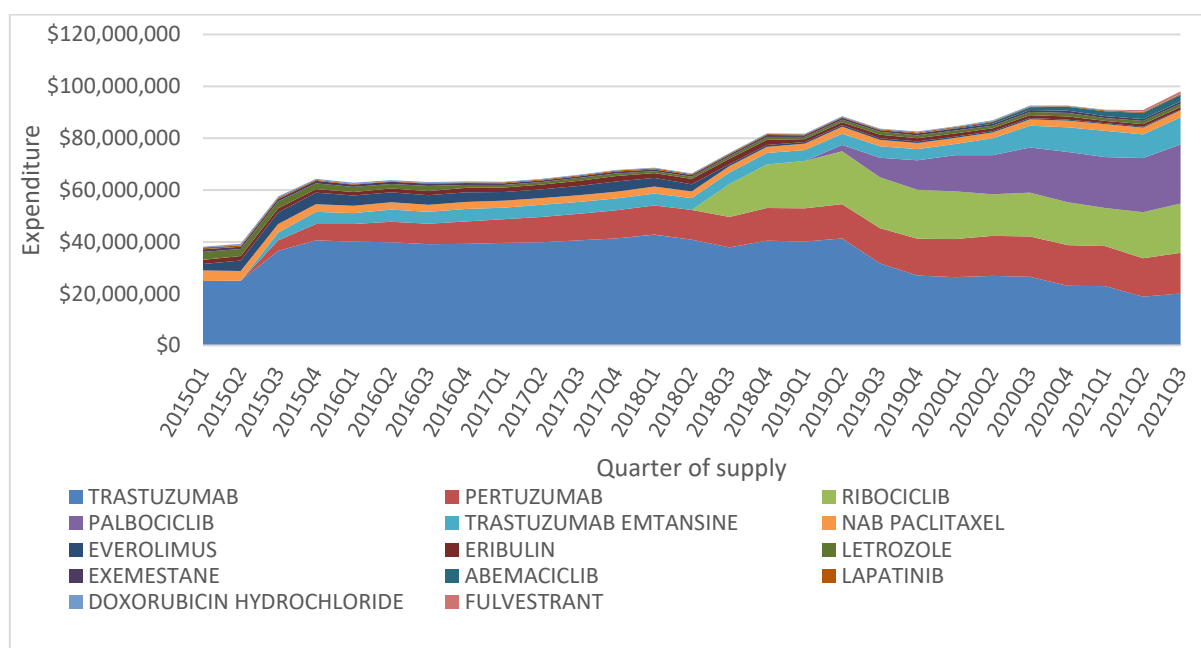


Figure 2b: Total Government expenditure on breast cancer drugs by quarter

Source: Services Australia prescriptions database, extracted December 2021

Note: All figures are based on published prices and are net of patient co-payments. Some medicines have special pricing arrangements and government expenditure may be less than presented.

Figures 2a and 2b shows that government expenditure, based on the published list prices, is mainly spent on five of the BC medicines (trastuzumab, pertuzumab, ribociclib, palbociclib and trastuzumab emtansine). Figure 2a shows that trastuzumab has recorded a significant fall in government expenditure since 2019 Q2 and palbociclib had the highest expenditure in 2021 Q2, when it overtook trastuzumab. Government expenditure on ribociclib is just fractionally lower than trastuzumab.

Several price reductions have been applied to the BC listings over time, refer to Appendix 1 for a summary of the pricing changes. As such, the growth in expenditure on BC medicines has been gradual in particular from the reduction in the cost of trastuzumab (Figure 2b).

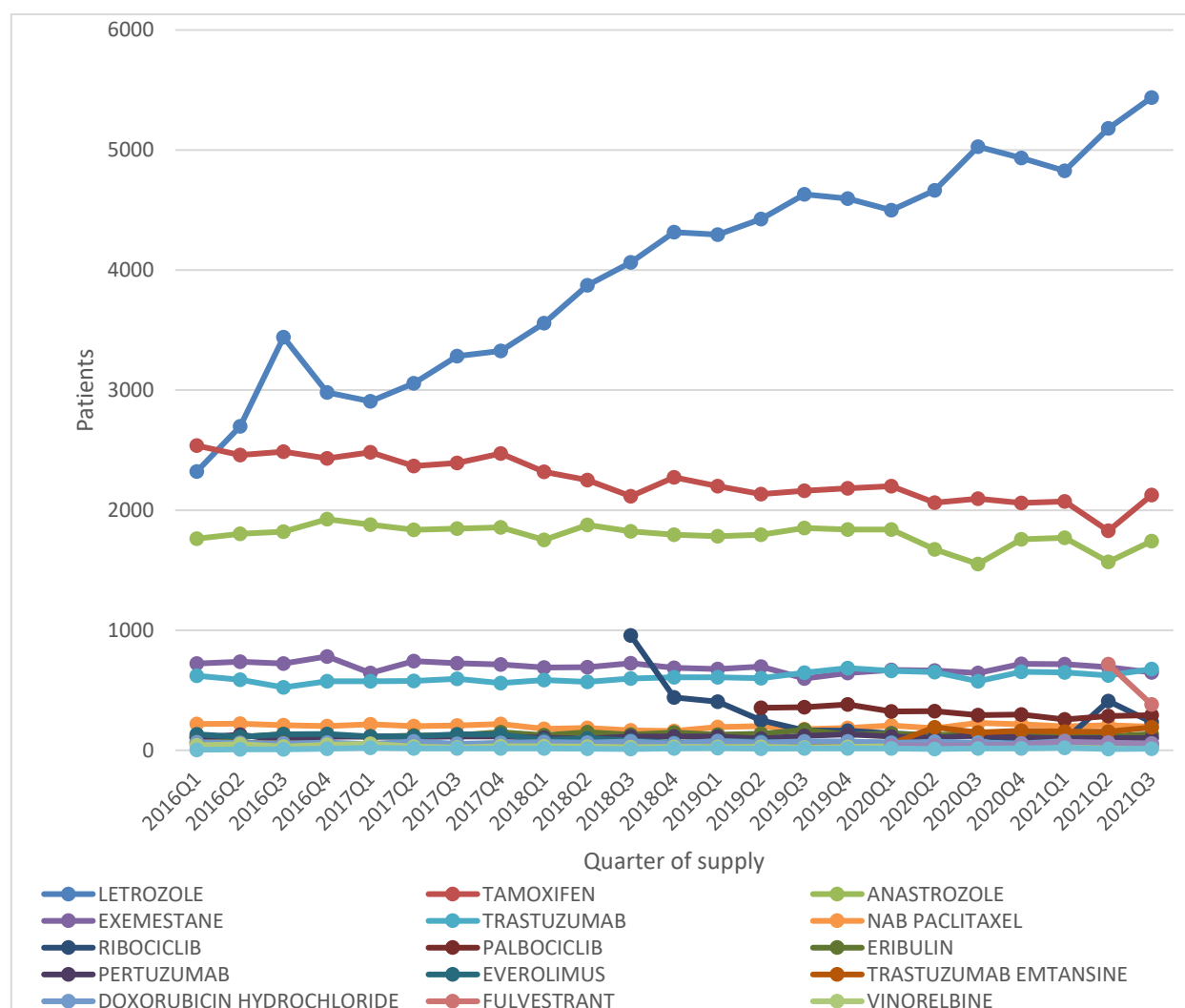


Figure 3a: Initiating patients supplied breast cancer drugs per quarter

Source: Services Australia prescriptions database, extracted December 2021

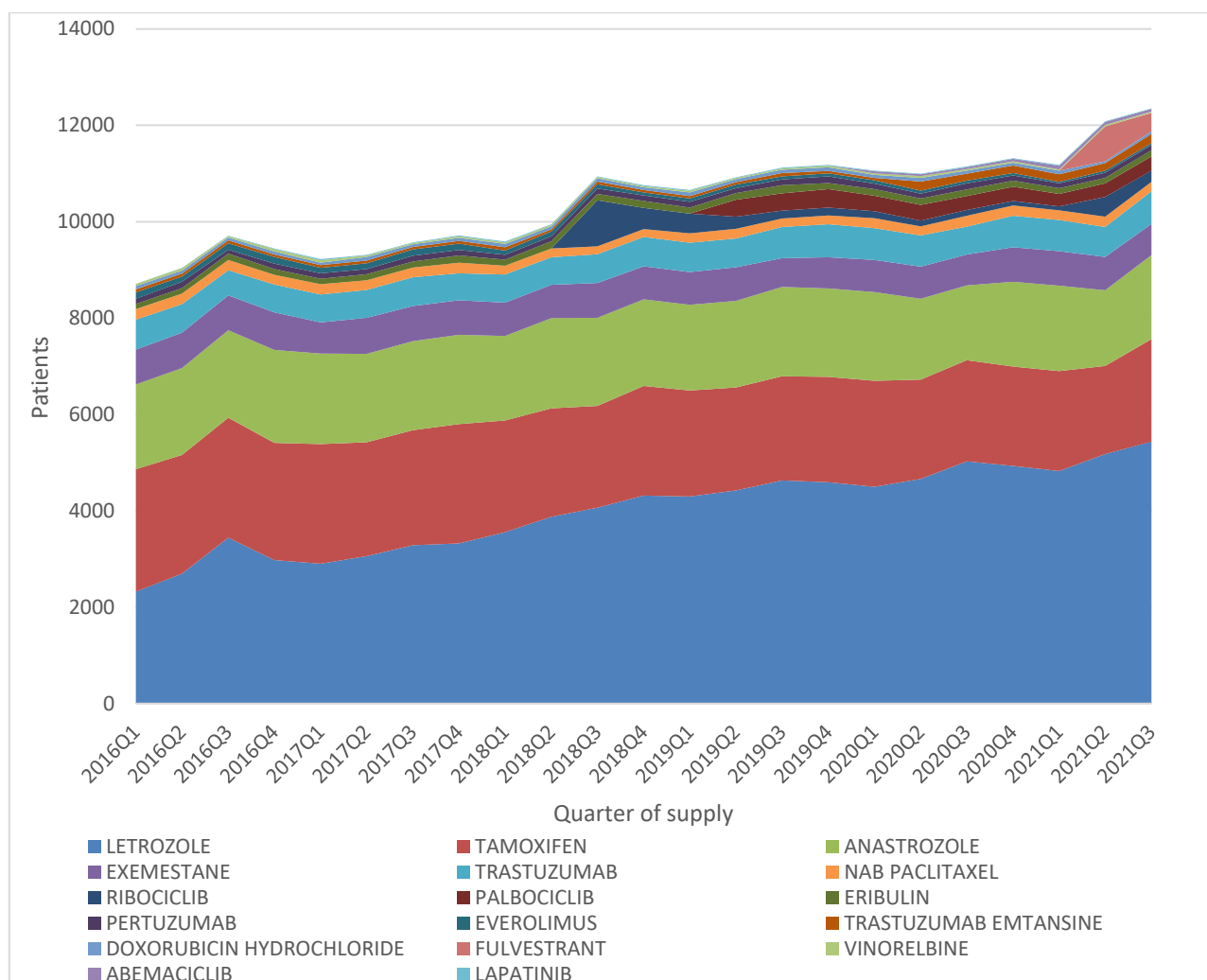


Figure 3b: Total initiating patients supplied breast cancer drugs per quarter

Source: Services Australia prescriptions database, extracted December 2021

Since 2016 Q2 most BC patients have initiated on letrozole (2021 Q3 - 5,438 patients). The next highest initiating BC drug is tamoxifen (2021 Q3 - 2,126 patients), followed by anastrozole (2021 Q3 - 1,742). These drugs are examined further in the Hormone Modulating medicines section.

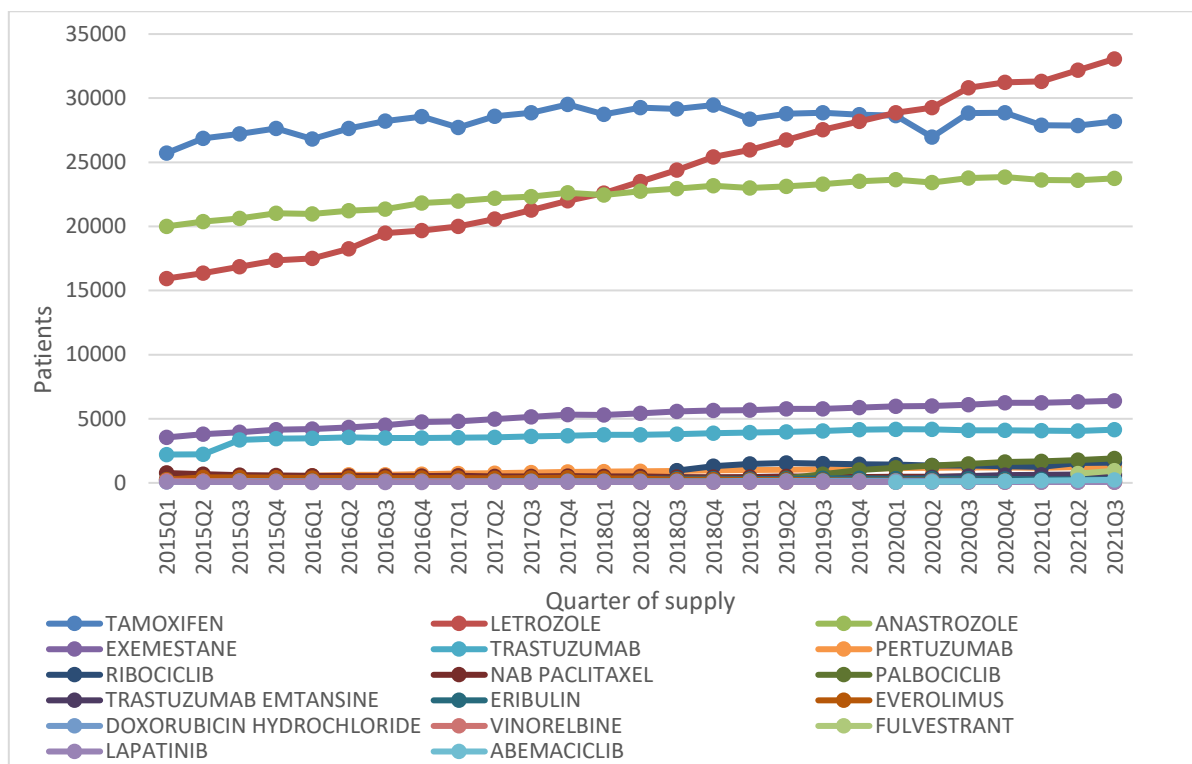


Figure 4a: Prevalent patients supplied breast cancer drugs per quarter

Source: Services Australia prescriptions database, extracted December 2021

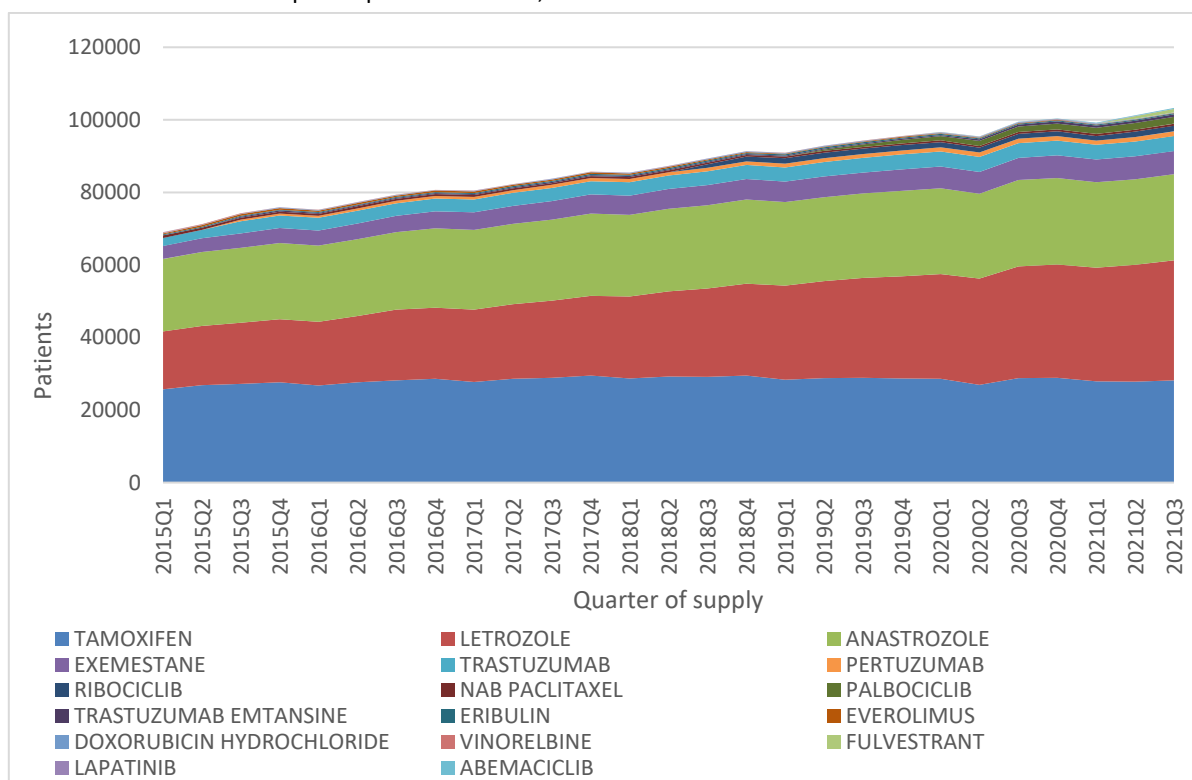


Figure 4b: Total prevalent patients supplied breast cancer drugs per quarter

Source: Services Australia prescriptions database, extracted December 2021

Similar to initiating BC patients, since 2015 most prevalent patients were supplied the three hormone modulating medicines, letrozole (2021 Q3 – 33,060 patients), tamoxifen (2021 Q3 – 28, 119 patients), and anastrozole (2021 Q3 – 23,749) (Figure 4a and 4b). The rates of growth in the number of patients supplied tamoxifen and anastrozole are stable, while the rate of growth in patients supplied letrozole has increased over time.

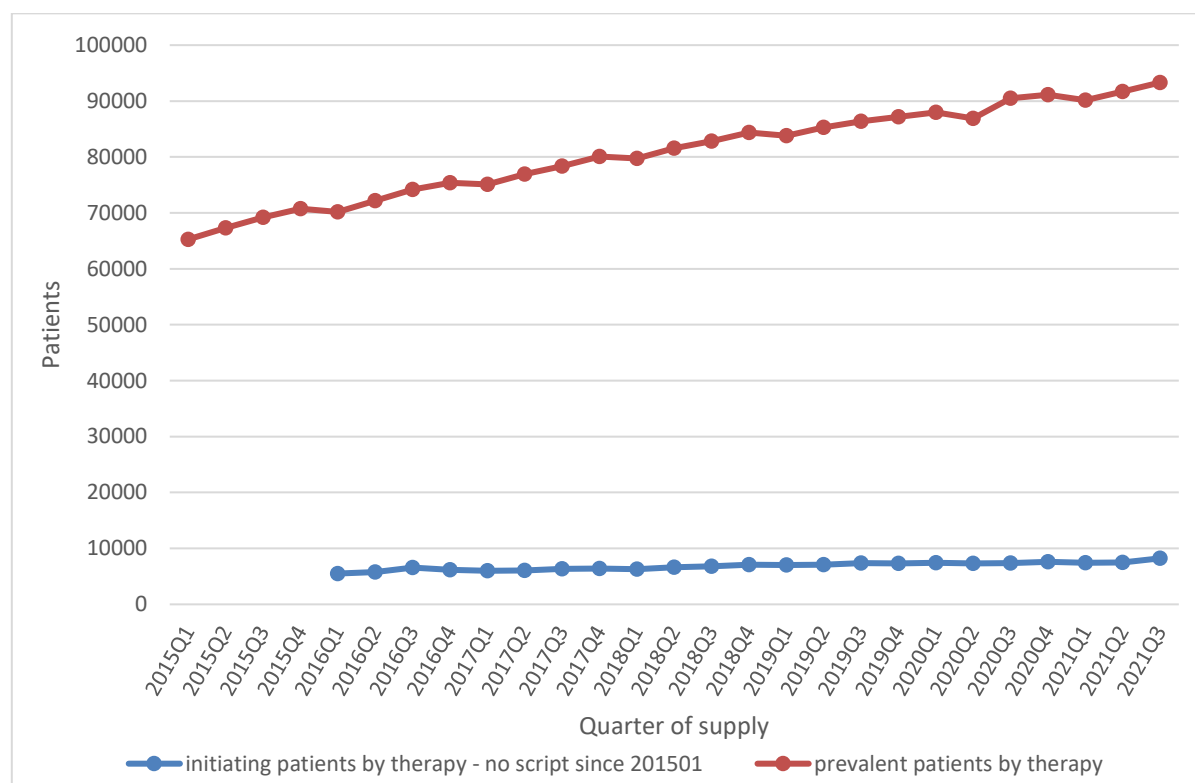


Figure 5: Initiating and prevalent breast cancer patients by quarter

Source: Services Australia prescriptions database, extracted December 2021

Figure 5 shows that the number of initiating BC patients has remained stable since 2016 Q1 while the number of prevalent patients has increased.

Hormone modulating medicines

Figures 3a, 3b, 4a and 4b show that hormone modulating medicines are the most frequently supplied BC drugs.

Figure 6a and 6b show that the utilisation of hormone modulation BC medicines is increasing. In 2018 Q4 letrozole overtook anastrozole as the highest prescribed hormone modulating medication.

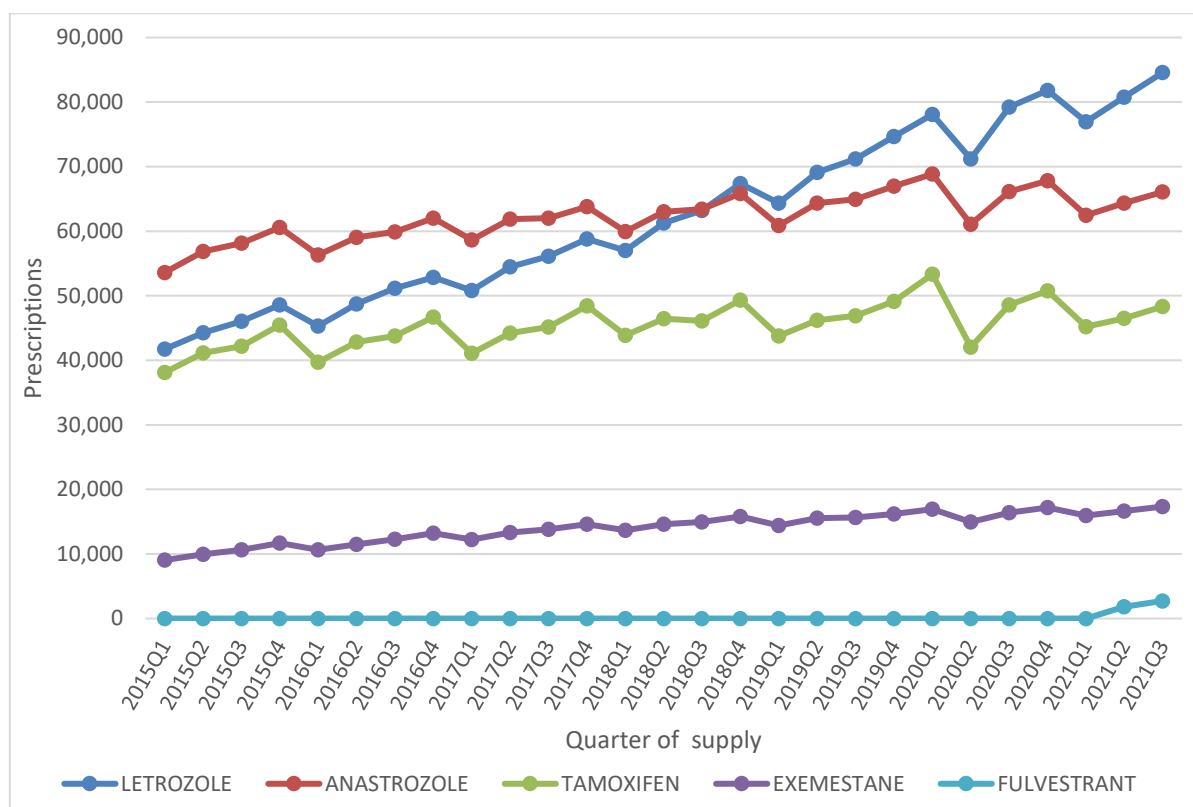


Figure 6a: Number of prescriptions for hormone modulating medicines by quarter

Source: Services Australia prescriptions database, extracted December 2021

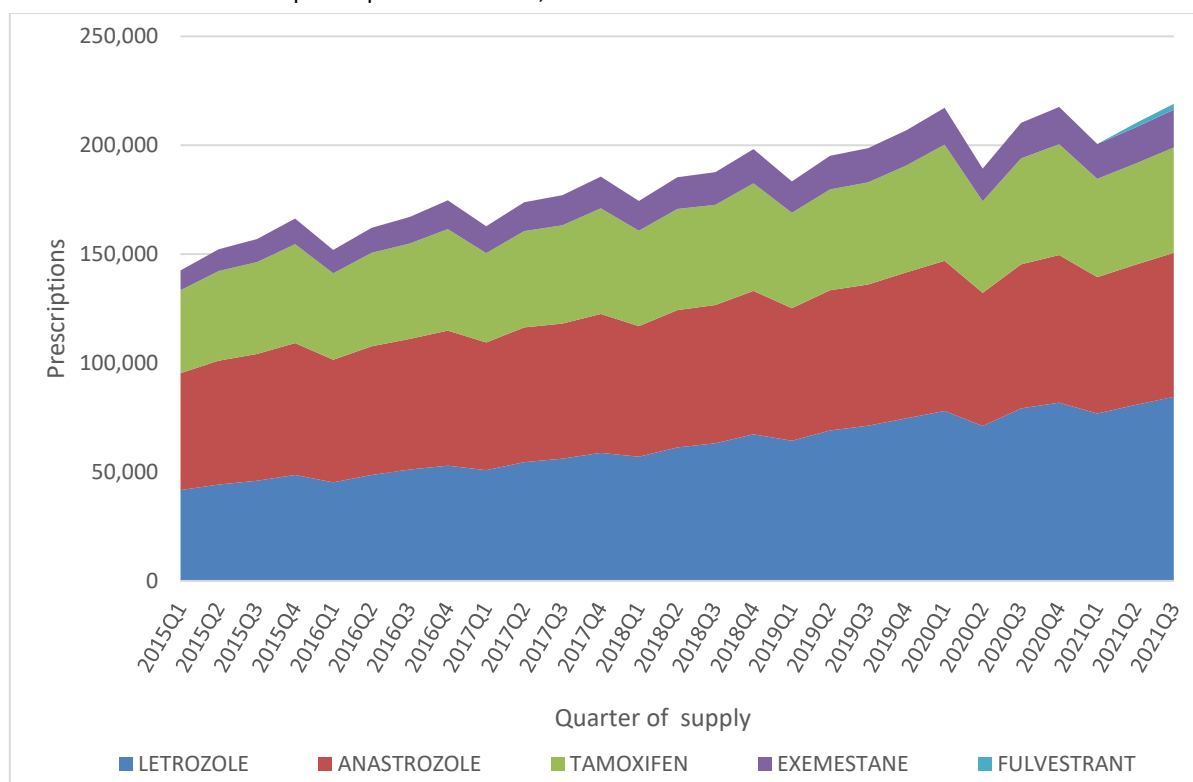


Figure 6b: Total number of prescriptions for hormone modulating medicines by quarter

Source: Services Australia prescriptions database, extracted December 2021

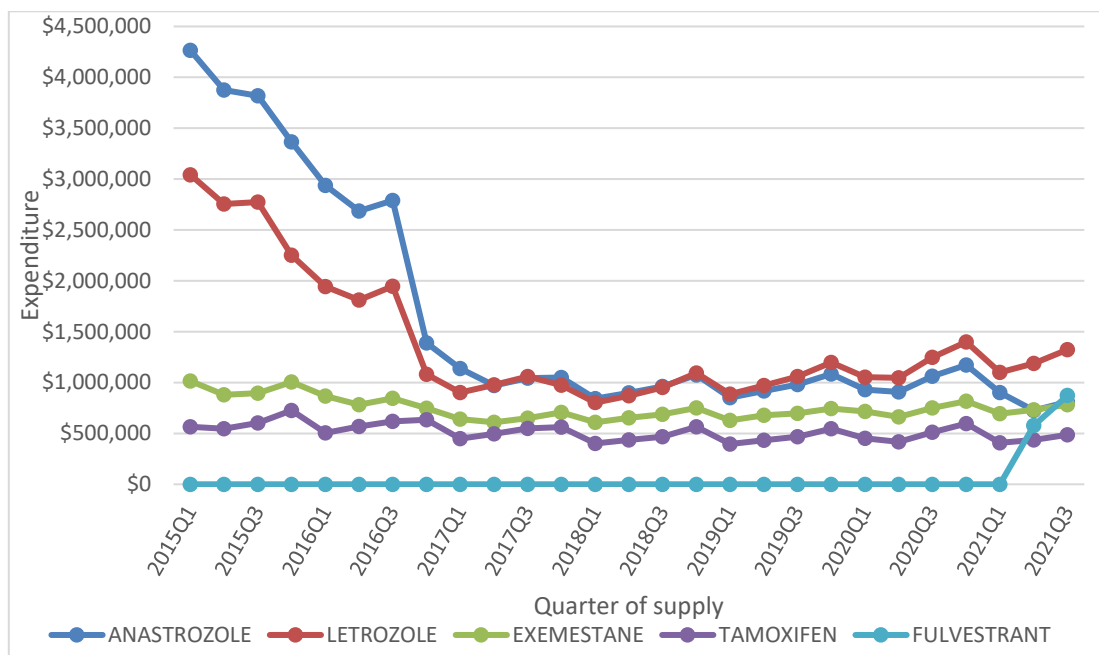


Figure 6c: Expenditure of hormone modulating medicines by quarter

Source: Services Australia prescriptions database, extracted December 2021

Note: All figures are based on published prices and are net of patient co-payments. Some medicines have special pricing arrangements and government expenditure may be less than presented.

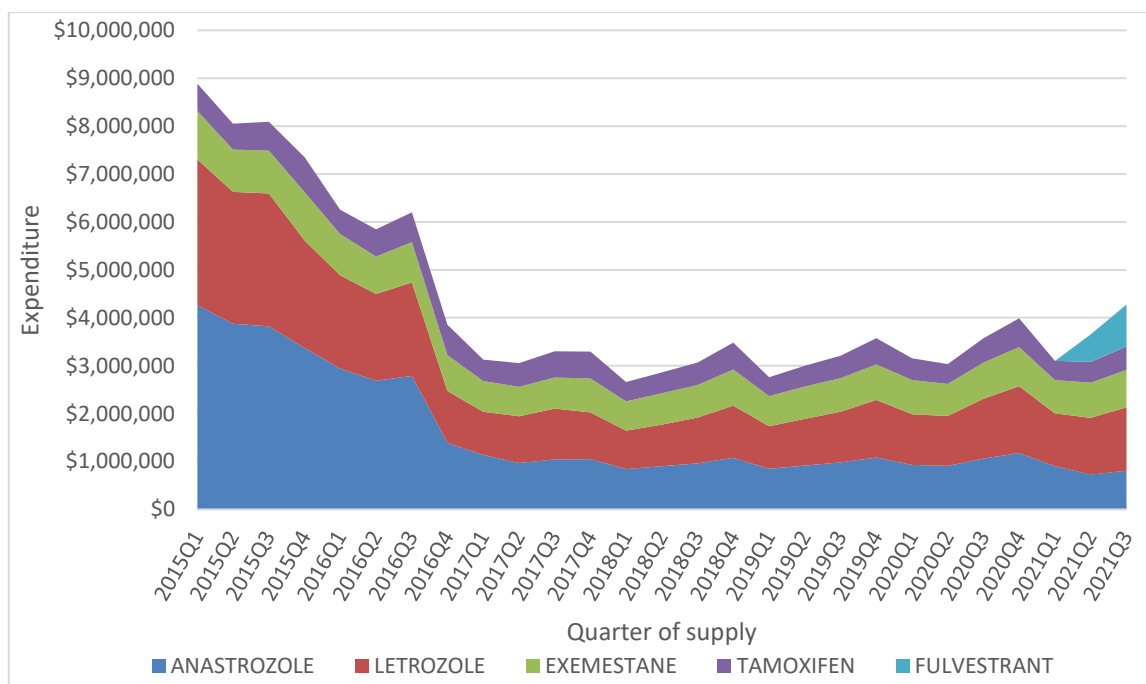


Figure 6d: Total expenditure of hormone modulating medicines by quarter

Source: Services Australia prescriptions database, extracted December 2021

Note: All figures are based on published prices and are net of patient co-payments. Some medicines have special pricing arrangements and government expenditure may be less than presented.

Price reductions have applied for anastrozole, letrozole, exemestane and tamoxifen. As such, government expenditure on hormone modulating BC treatments has significantly reduced over time and has stabilised since 2017 (Figure 6d). The number of prescriptions supplied has increased from a total of 142,507 prescriptions in 2015 Q1 to 173,911 prescriptions in 2017 Q2 - a growth rate of around 22%.

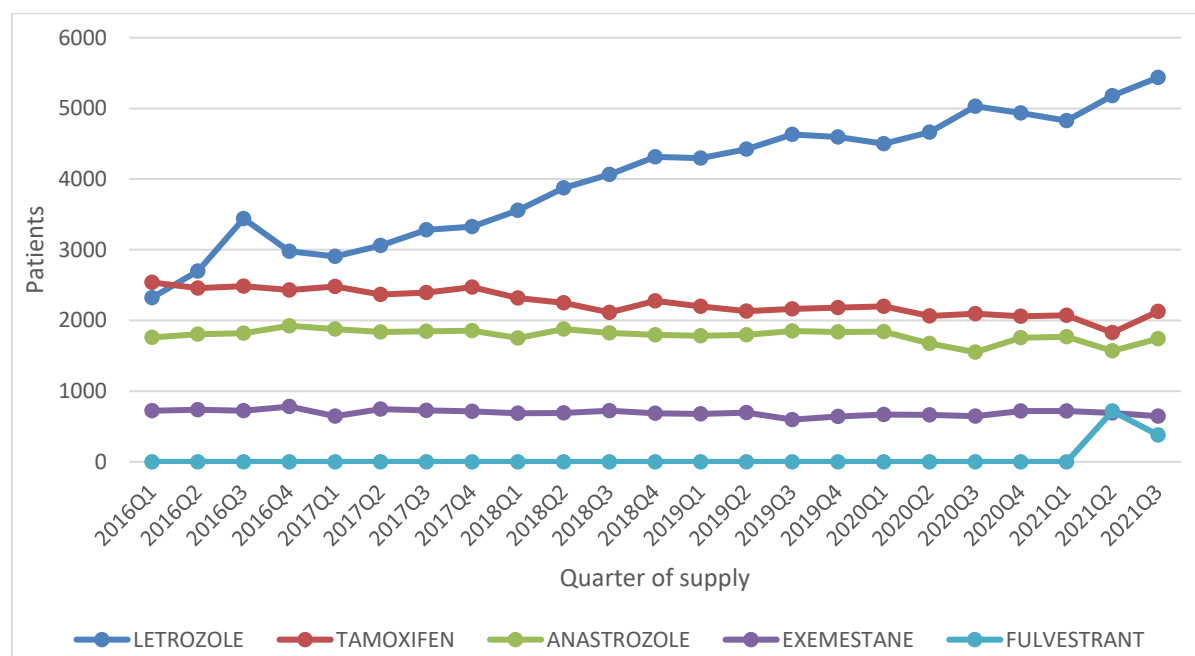


Figure 6e: Patients initiating treatment on hormone modulating medicines by quarter

Source: Services Australia prescriptions database, extracted December 2021

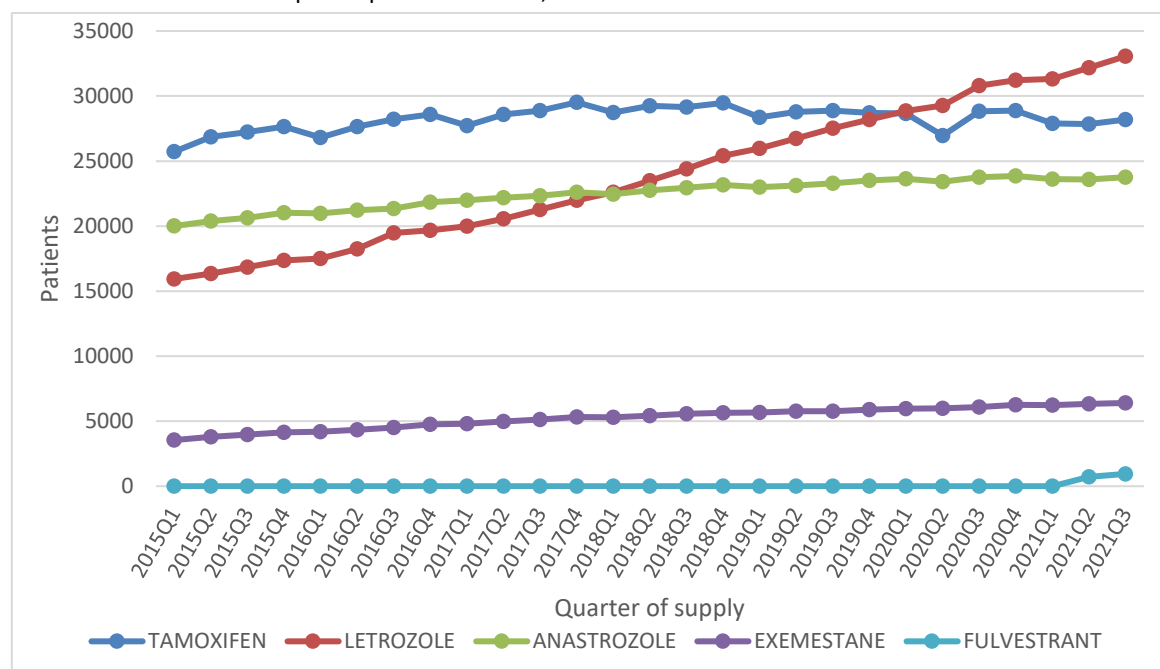


Figure 6f: Patients continuing treatment on hormone modulating medicines by quarter (prevalent)

Source: Services Australia prescriptions database, extracted December 2021

Most patients were initiated on letrozole, with its utilisation in initiating patients increasing over time. Compared to letrozole, the other hormone modulating medicines trajectories appear to have stabilised or have slow rates of growth (Figure 6e).

Letrozole started off as the third most supplied medication in prevalent BC patients, with tamoxifen and anastrozole having higher prescription counts, however since 2020 Q1 letrozole has become the most prescribed hormone modulating BC drug for prevalent patients (Figure 6f).

Protein kinase modulators

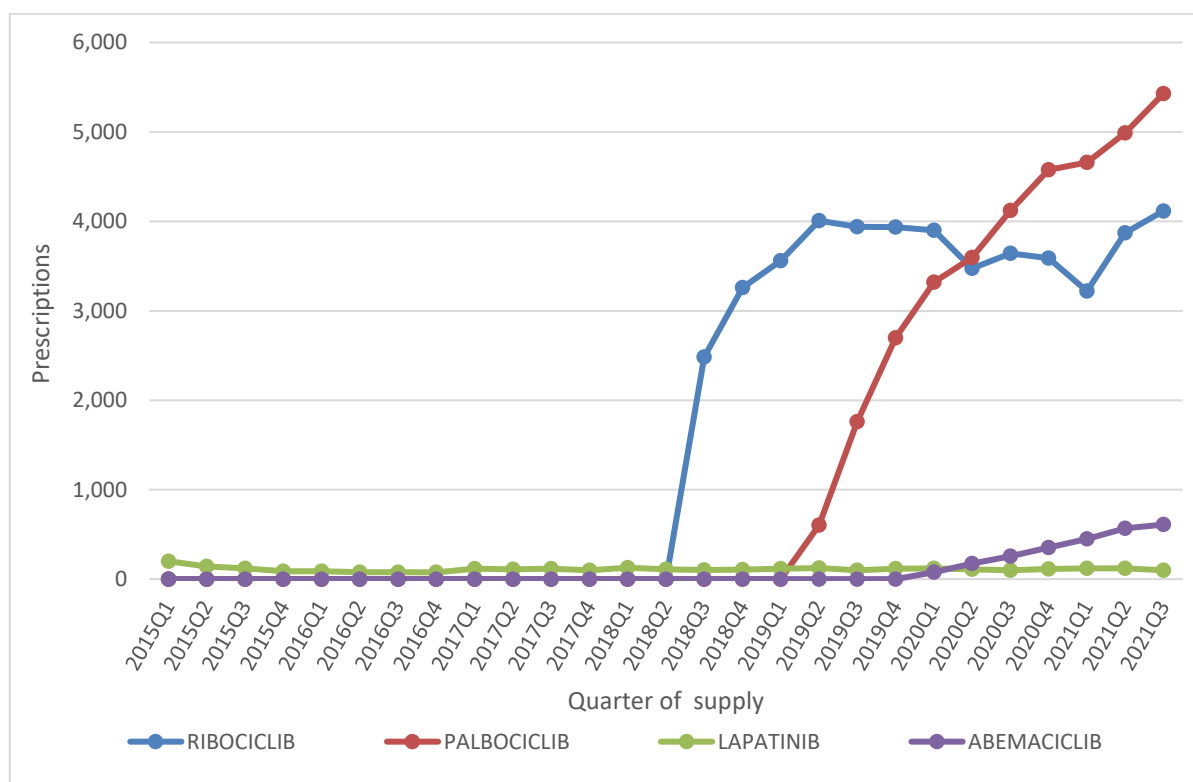


Figure 7a: Number of prescriptions for protein kinase modulators by quarter

Source: Services Australia prescriptions database, extracted December 2021

Upon listing, ribociclib started at 2,483 prescriptions in 2018 Q3, and its use has grown since then with 4,117 prescriptions supplied in 2021 Q3.

Palbociclib's utilisation shows a steady increase since listing in 2019 Q2 with 603 prescriptions, to 5,430 prescriptions recorded in 2021 Q3. This rate is much higher than its predicted use, discussed further below.

The utilisation of ribociclib and palbociclib seen in Figure 7a and 7b is low relative to letrozole, anastrozole and tamoxifen (Figures 1a, 1b and Table 1).

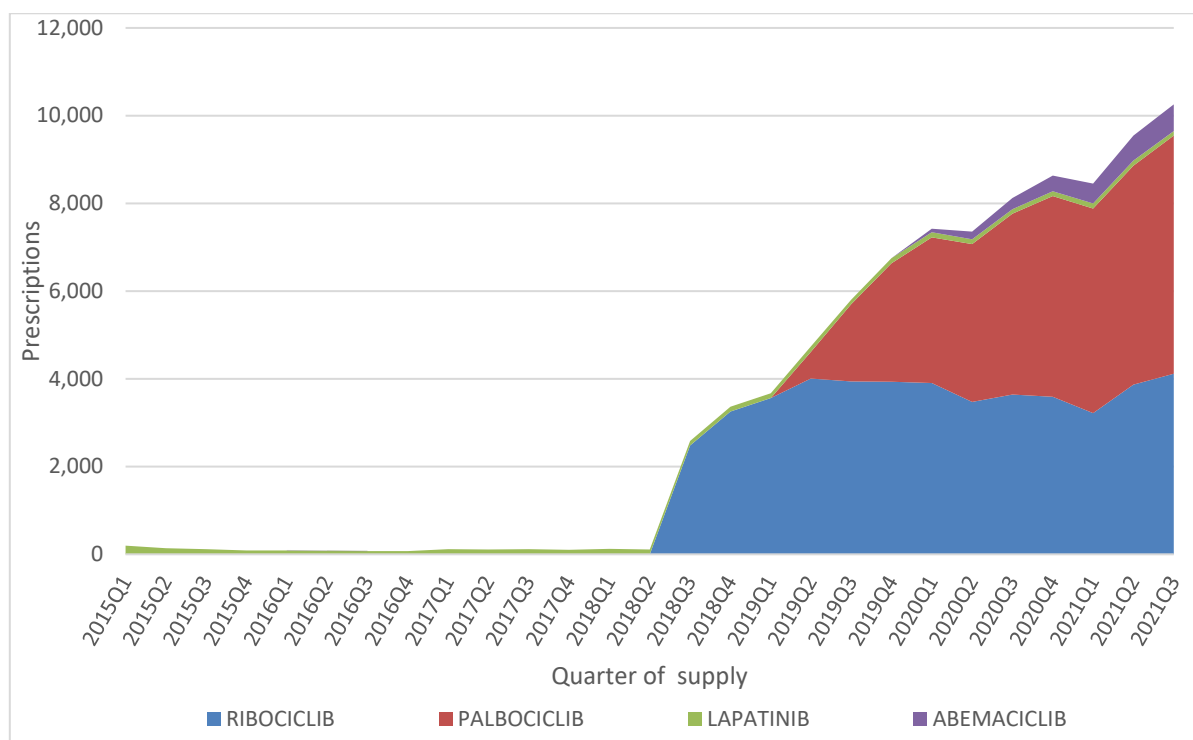


Figure 7b: Total number of prescriptions for protein kinase modulators by quarter

Source: Services Australia prescriptions database, extracted December 2021

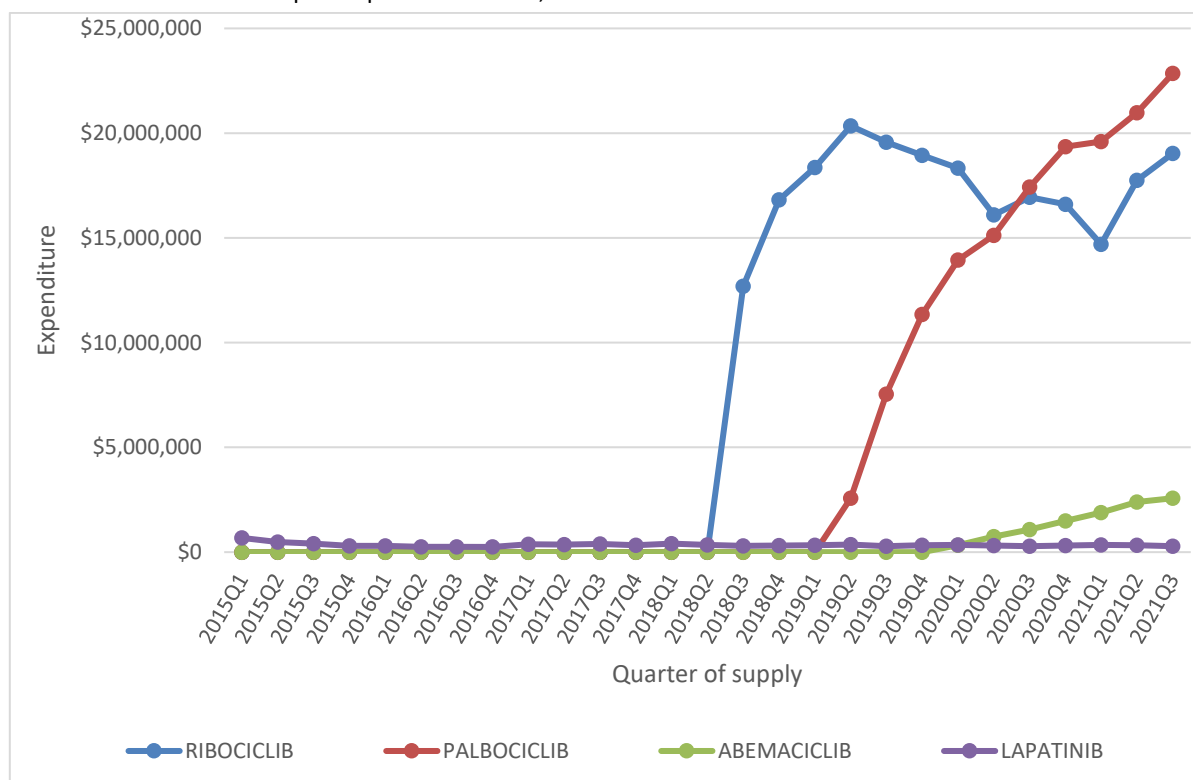


Figure 7c: Expenditure for protein kinase modulators by quarter

Source: Services Australia prescriptions database, extracted December 2021

Note: All figures are based on published prices and are net of patient co-payments. Some medicines have special pricing arrangements and government expenditure may be less than presented.

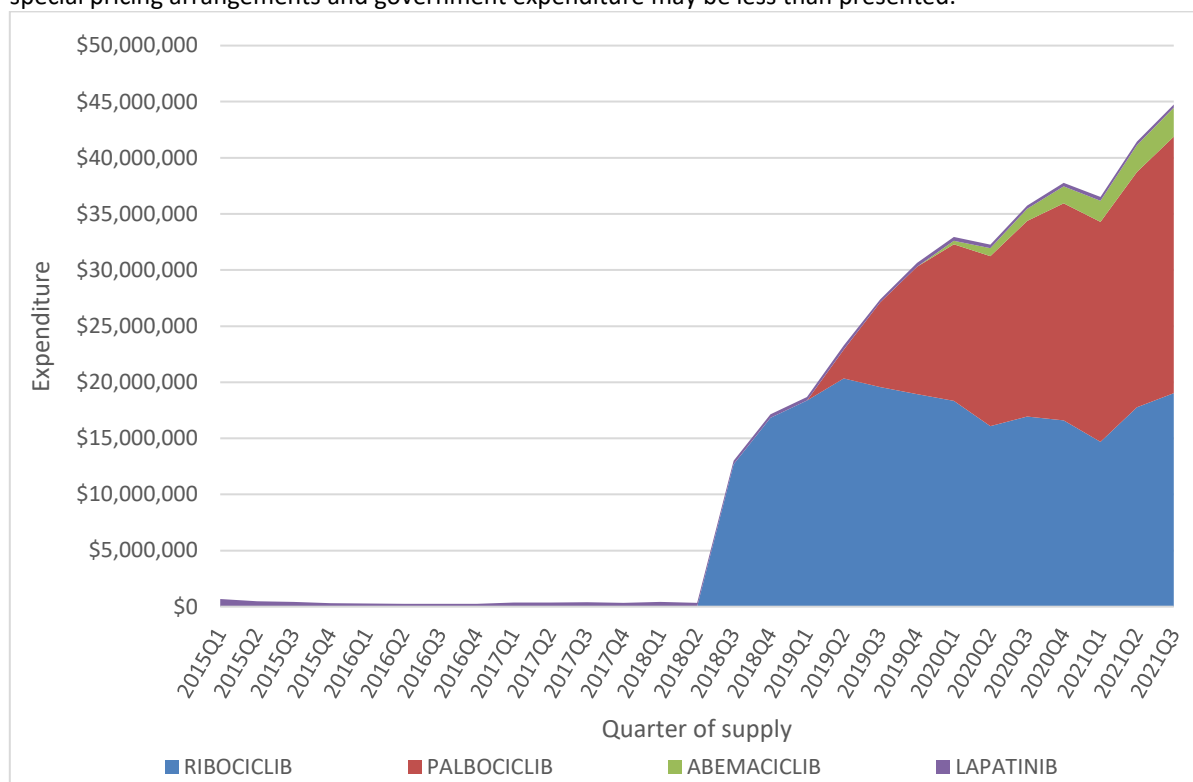


Figure 7d: Total expenditure for protein kinase modulators by quarter.

Source: Services Australia prescriptions database, extracted December 2021

Note: All figures are based on published prices and are net of patient co-payments. Some medicines have special pricing arrangements and government expenditure may be less than presented.

Expenditure on protein kinase modulators has significantly increased since ribociclib and palbociclib were listed on the PBS. Of all BC drugs, palbociclib has highest PBS expenditure based on the published list prices, whilst ribociclib was third highest, just fractionally lower than trastuzumab (Figure 2a).

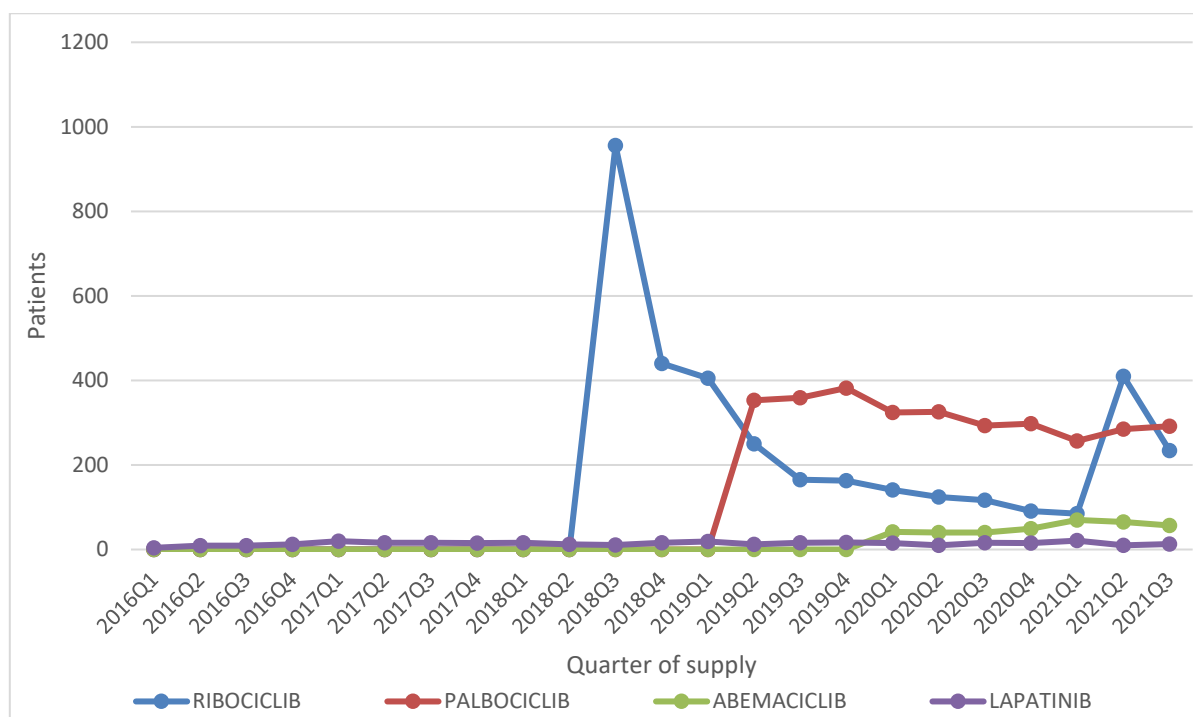


Figure 7e: Patients initiating treatment on protein kinase modulators by quarter

Source: Services Australia prescriptions database, extracted December 2021

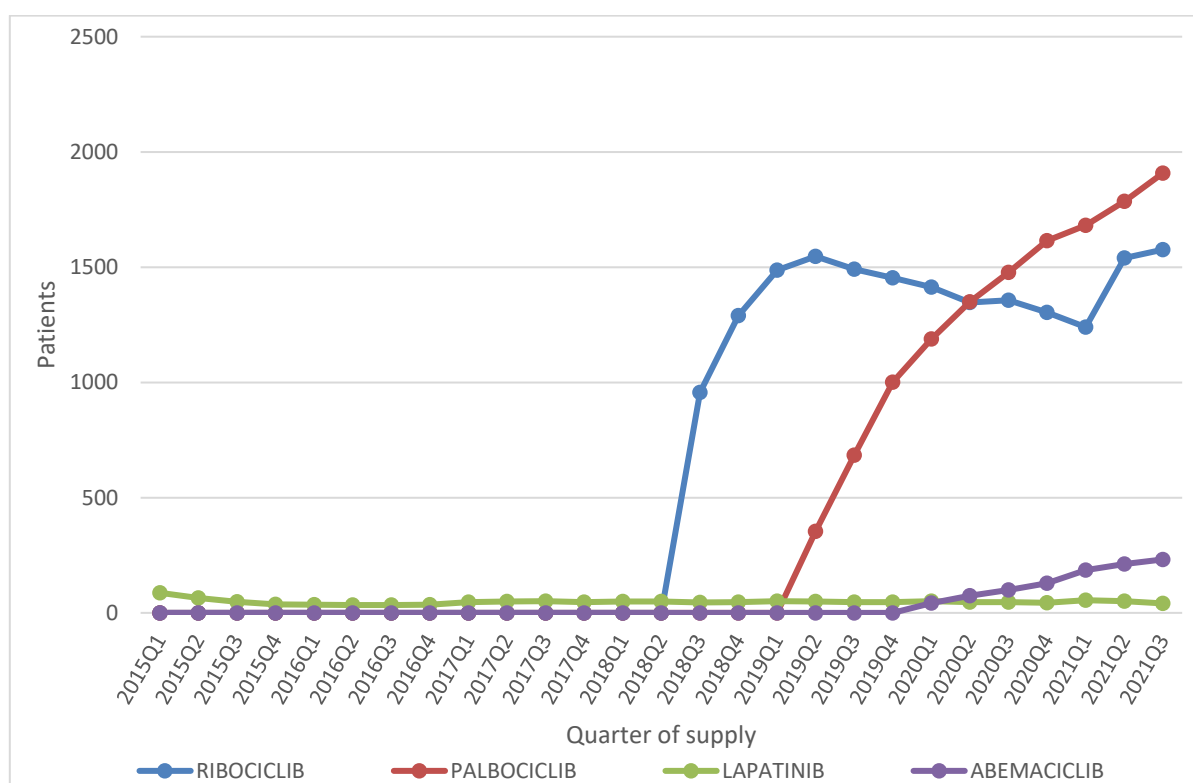


Figure 7f: Patients continuing treatment on protein kinase modulators by quarter (prevalent)

Source: Services Australia prescriptions database, extracted December 2021

Ribociclib and Palbociclib are the most commonly supplied protein kinase modulators. Palbociclib was listed in 2019 Q2, with 353 prevalent patients, by 2021 Q3 the amount of prevalent patients being treated with Palbociclib had risen to 1,908. By 2020 Q2 the use of palbociclib has reached parity with ribociclib (1,349 vs 1,356 respectively). Since that point the use of palbociclib in prevalent patients has overtaken the use of ribociclib.

Utilisation of chemotherapy and immunotherapy for breast cancer

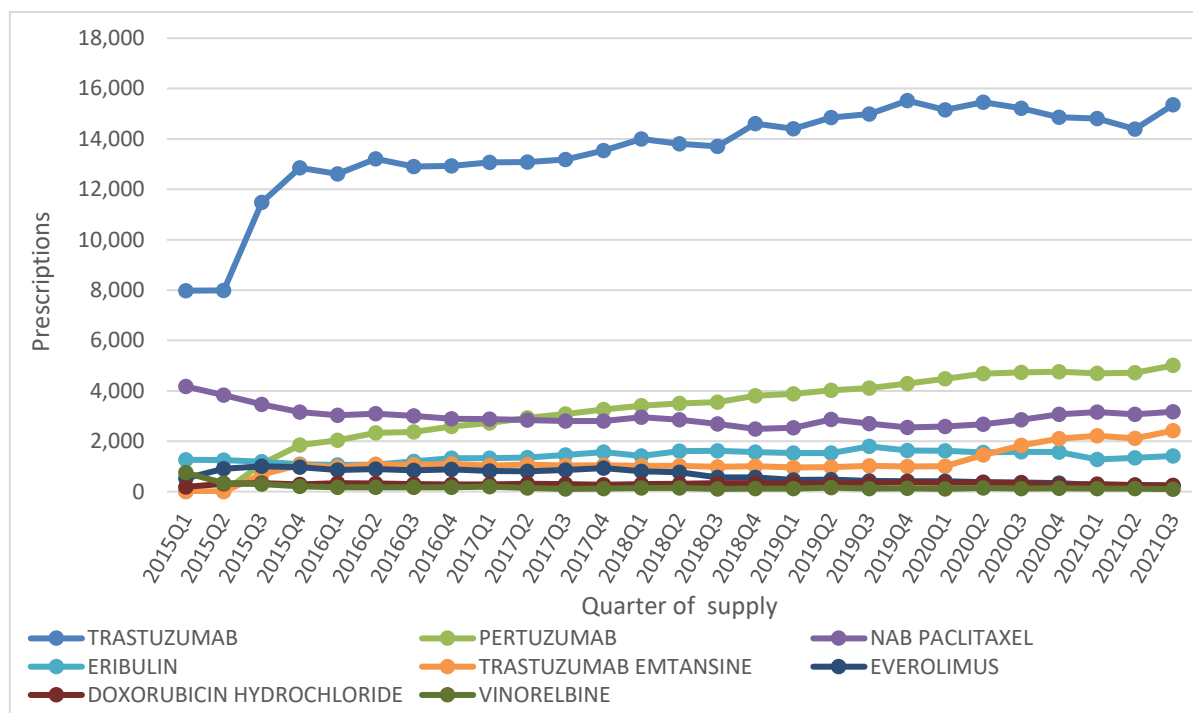


Figure 8a: Number of chemotherapy and immunotherapy prescriptions supplied

Source: Services Australia prescriptions database, extracted December 2021

The supply of chemotherapy and immunotherapy listings has stabilised (Figure 8a). Out of the remaining medicines, trastuzumab is the most supplied. The utilisation of trastuzumab increased upon the closure of the Herceptin Program in 2015 Q2 and its utilisation as plateaued since 2019 Q4 (Figure 8a).

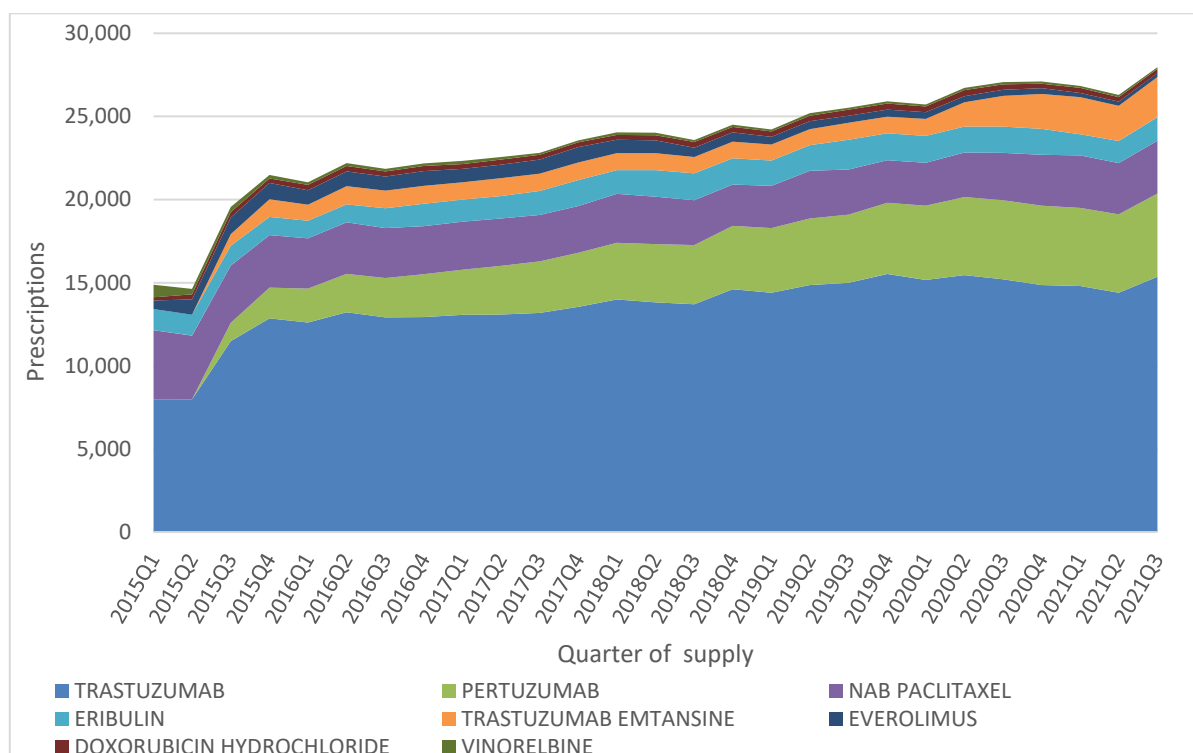


Figure 8b: Total number prescriptions supplied for the remaining breast cancer drugs including chemotherapy and immunotherapy

Source: Services Australia prescriptions database, extracted December 2021

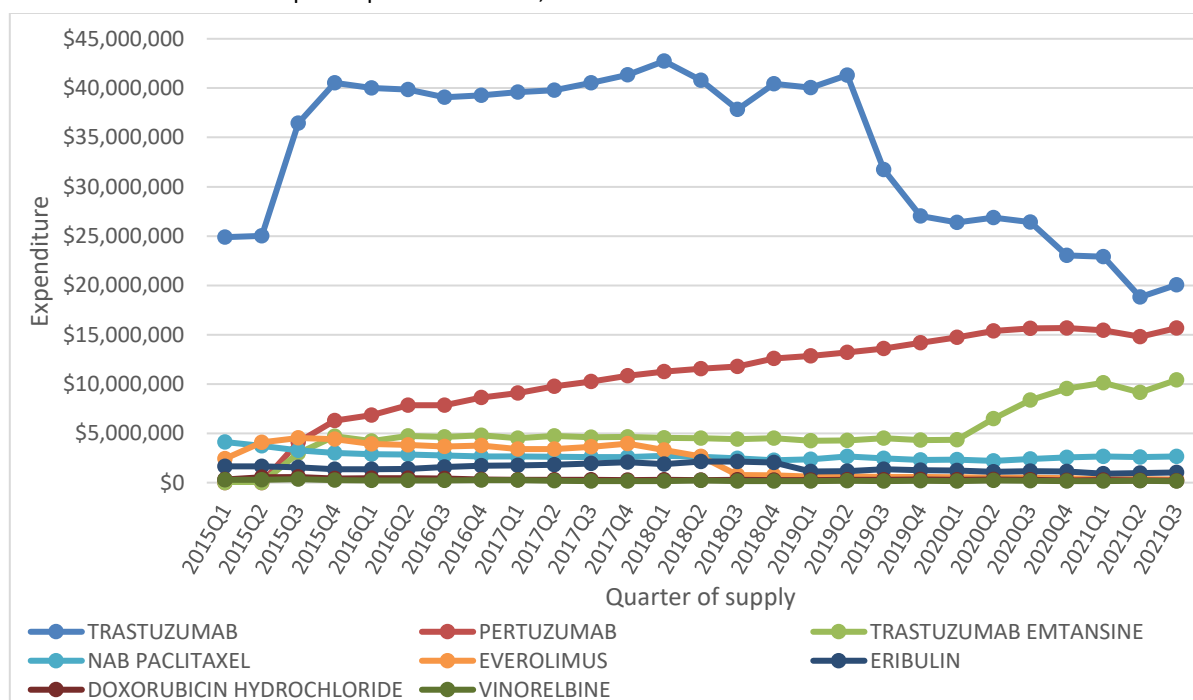


Figure 8c: Expenditure on the remaining breast cancer drugs including chemotherapy and immunotherapy

Source: Services Australia prescriptions database, extracted December 2021

Note: All figures are based on published prices and are net of patient co-payments. Some medicines have special pricing arrangements and government expenditure may be less than presented.

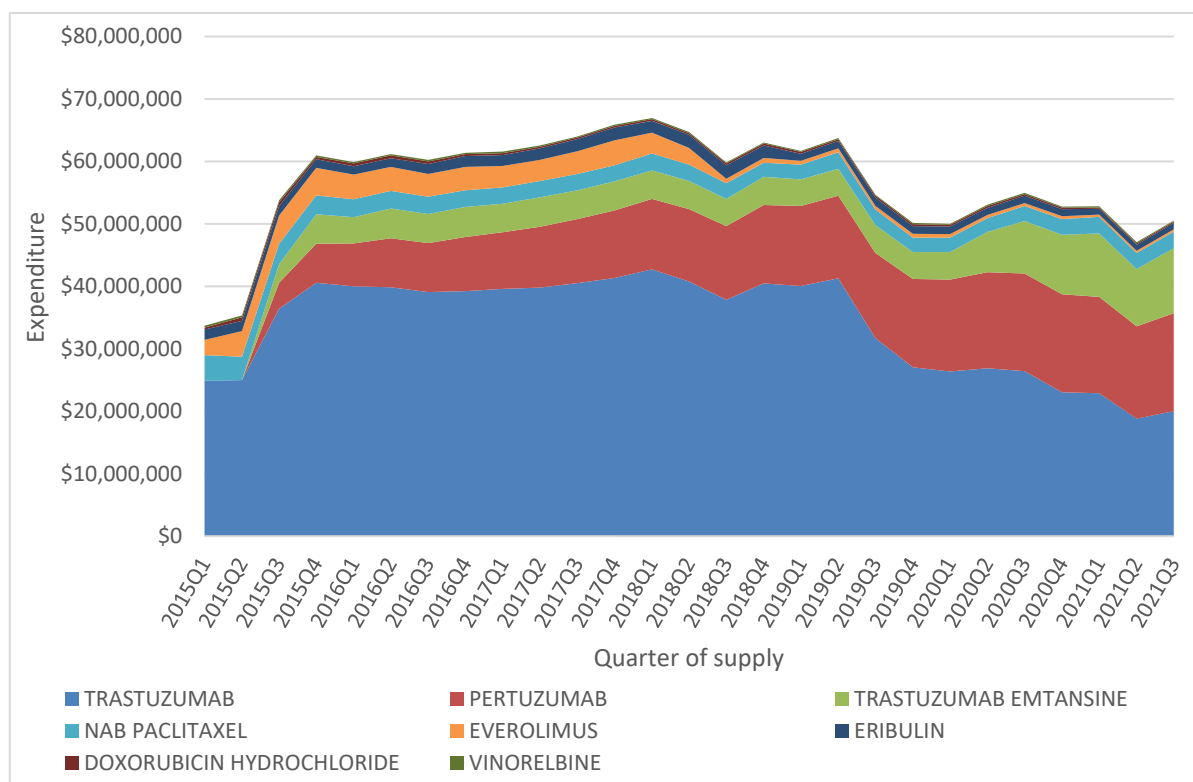


Figure 8d: Total expenditure of the remaining breast cancer drugs including chemotherapy and immunotherapy

Source: Services Australia prescriptions database, extracted December 2021

Note: All figures are based on published prices and are net of patient co-payments. Some medicines have special pricing arrangements and government expenditure may be less than presented.

Despite the utilisation of these medicines remaining relatively stable, government expenditure on BC listings has fallen since 2015 Q3. This fall in expenditure can mainly be attributed to a decrease in the price of trastuzumab (refer to Appendix 1 for details of price reductions which have been applied to trastuzumab).

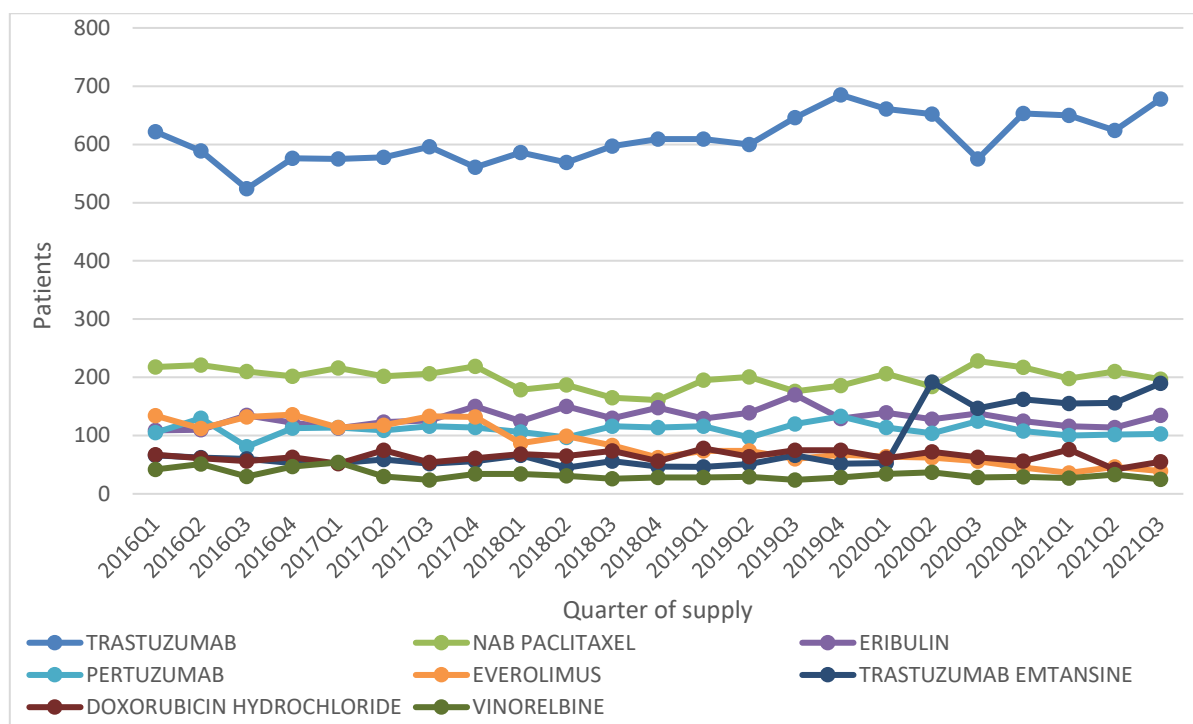


Figure 8e: Patients initiating treatment on chemotherapy and immunotherapy by quarter

Source: Services Australia prescriptions database, extracted December 2021

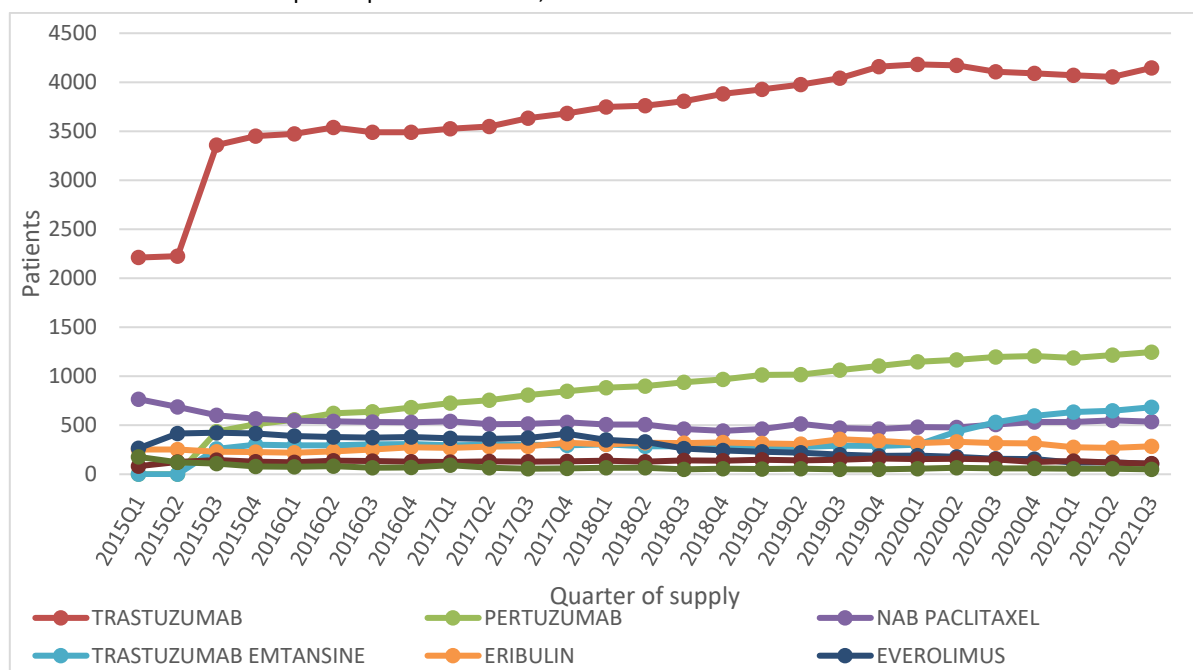


Figure 8f: Patients continuing treatment on chemotherapy and immunotherapy by quarter (prevalent)

Source: Services Australia prescriptions database, extracted December 2021

Trastuzumab is the most commonly used medicine for initiating and prevalent patients in this remaining group.

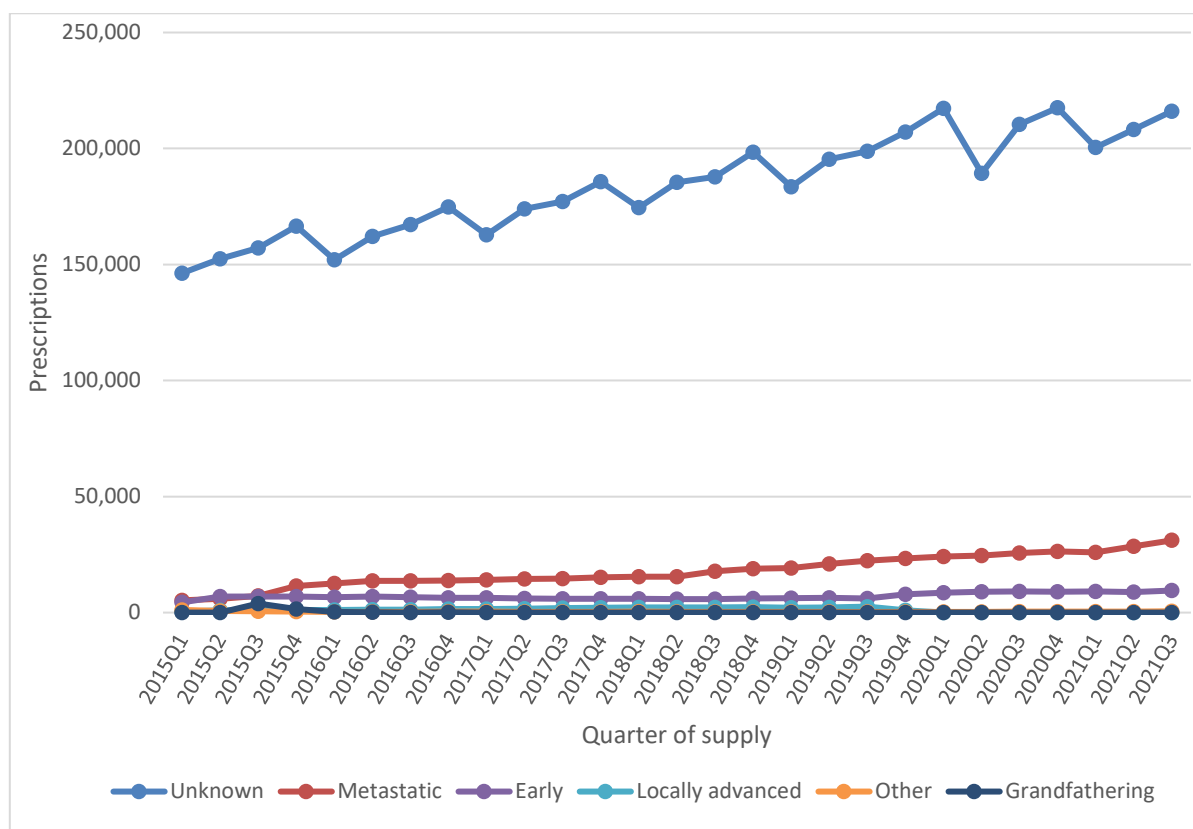


Figure 9a: Prescriptions by breast cancer stage

Source: Services Australia prescriptions database, extracted December 2021

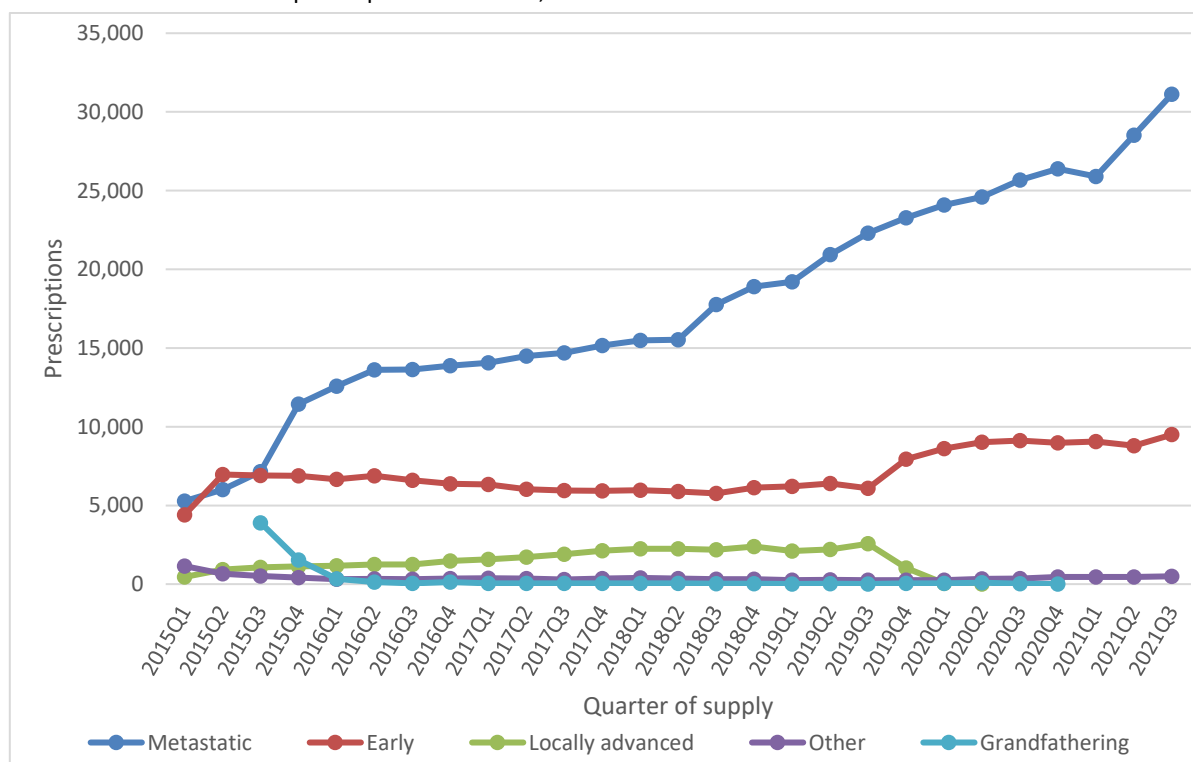


Figure 9b: Prescriptions by breast cancer stage with “unknown removed”

Source: Services Australia prescriptions database, extracted December 2021

Analysis of actual versus predicted utilisation

Approach taken to estimate utilisation

The PBAC considered palbociclib at the March 2018 meeting where the sponsor used a previously established epidemiological approach to estimating utilisation from the November 2017 submission for palbociclib. This approach used the incidence of BC from the Australian Institute of Health and Welfare (AIHW) followed by the proportion of patients at various stages in diagnosis using data from Walters et al. 2013 and DUSC advice from the March 2017 submission.

Following the PBS listing of ribociclib on 1 July 2018 the approach to estimating the utilisation of palbociclib changed from an epidemiological approach to a market share approach and estimated palbociclib would take approximately ■ of the market.

This analysis compares the predicted and actual use of use of palbociclib. The predicted use was extracted from final agreed estimates between the sponsor and the Department of Health.

Table 2: Predicted vs Actual analysis – Palbociclib

Palbociclib listing years		Year 1	Year 2
		May 2019- April 2020	May 2020 - April 2021
Patients	Actual	1,540	2,261
	Predicted		
Prescriptions	Actual	9,515	17,398
	Difference		
	Predicted		
Net Cost PBS/RPBS	Actual	\$40,172,870	\$73,354,351
	Difference		
	Predicted		

Note: the predicted and actual figures are based on the published price

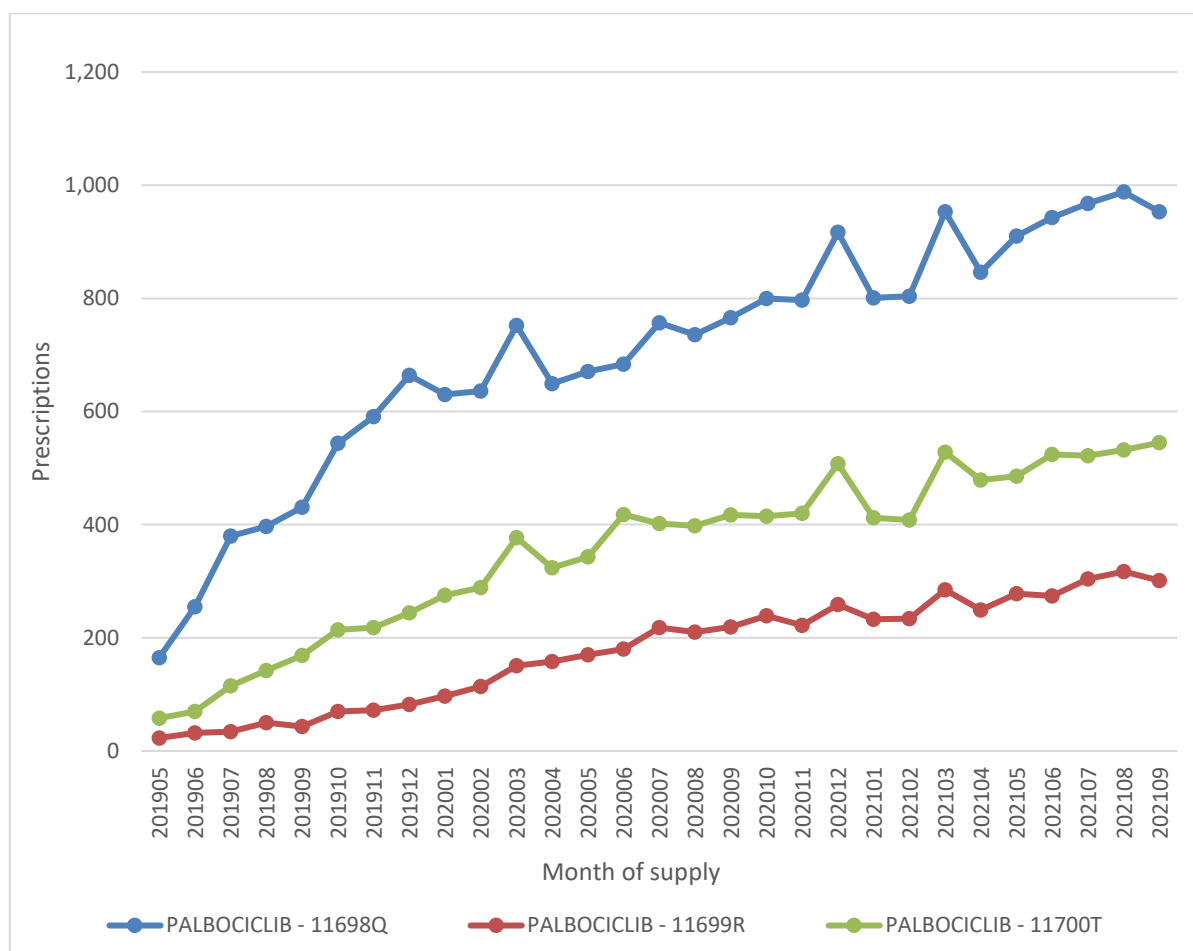


Figure 10: Prescriptions of palbociclib supplied by quarter

Source: Services Australia prescriptions database, extracted December 2021

The number of prescriptions supplied for palbociclib has exceeded the predicted use in year one and two of listing. The submission estimated that palbociclib would take [REDACTED] of ribociclib's market, however when comparing the number of prescriptions supplied for these medicines (Figure 7a) it is apparent that this has not happened and that the listing of palbociclib has grown the protein kinase modulator market.

Discussion

Palbociclib was anticipated to substitute for the existing listing of ribociclib. The actual utilisation was significantly greater in its first two years of listing than expected. In Year 2 the number of scripts dispensed was 17,398 compared to the forecast of [REDACTED] scripts. Of all BC listings, palbociclib had the highest PBS expenditure based on the published list price as at Quarter 3 2021 (Figure 2a).

In Quarter 3 2021, there were 93,316 patients supplied a PBS listing to treat BC (Figure 5). Since Quarter 1 2020 the number of patients initiating on a PBS listing has been around 7,500 patients per quarter (Figure 5). There has been a gradual growth in the number of prevalent patients supplied PBS therapy over time (Figure 5). The majority of prescriptions were supplied for the treatment of metastatic BC (Figure 9b). Total government expenditure on BC listings had remained relatively stable since Quarter 3 2020. Price reductions have been applied to several PBS listings which reduced the growth in the cost to the PBS (Figure 2b). See Appendix 1 for further details about the price reductions which have been applied.

The most supplied BC listings were letrozole, anastrozole and tamoxifen (Figures 1a and 6a). These drugs have Restricted Benefits listings with a general indication for hormone receptor positive (HR+) breast cancer for letrozole and anastrozole, and the reduction in breast cancer risk for tamoxifen. As HR+ BC is the most common subtype, representing two-thirds of breast cancers, it was expected that the utilisation of these hormone modulating drugs would be higher relative to other BC listings. Letrozole, anastrozole and fulvestrant are also used in combination with protein kinase inhibitors, including palbociclib, ribociclib and abemaciclib. Relative to letrozole, anastrozole and tamoxifen, the utilisation of exemestane and fulvestrant was lower due to their more restricted populations (Figure 6f). Exemestane is a Restricted Benefit listing for metastatic patients only who are HR+ and human epidermal growth factor receptor 2 (HER2) negative. Of the hormone modulating drugs, fulvestrant had the highest restriction level of Authority Required (STREAMLINED) and is listed for patients who have locally advanced or metastatic disease with HR+ and HER2 negative BC. Letrozole, anastrozole, tamoxifen, exemestane and fulvestrant have been subject to several price reductions over the analysis period (Appendix 1). As such, the PBS expenditure on these hormone blocking therapies was significantly less when compared to other drug classes, in particular when compared to listings of protein kinase modulators (Figures 2b and 6c).

The protein kinase inhibitors palbociclib, ribociclib and abemaciclib are General Schedule Authority Required listings for the treatment of locally advanced or metastatic HR+ HER2 negative BC. Lapatinib has a different General Schedule Authority Required listing that is restricted to HER2 positive patients with metastatic BC. As around 1 in 5 cases of BC are HER2 positive, the lower utilisation of lapatinib versus palbociclib, ribociclib and abemaciclib was expected (Figure 7a). As fulvestrant was a recent PBS listing at the time of analysis (from 1 April 2021), its utilisation was low (Figure 7a). Of all BC listings, palbociclib and ribociclib had the first and third highest PBS expenditure in Quarter 3 2021, respectively (Figure 2a).

The chemotherapy and immunotherapy listings for BC considered in this review include trastuzumab, trastuzumab emtansine, pertuzumab, NAB paclitaxel, everolimus, eribulin, doxorubicin hydrochloride and vinorelbine. Initiation of chemotherapy and immunotherapy was stable over time for most listings, with the exception of trastuzumab emtansine (Figure 8e). The increase in the utilisation of trastuzumab emtansine occurred after the extension of its listing to include early HER2 positive BC. The number of prevalent patients supplied chemotherapy or immunotherapy was stable (Figure 8f). The PBS expenditure on the chemotherapy and immunotherapy remained at a similar level since Quarter 3 2019, likely due to the application of price reductions to these listings (see Appendix 1).

DUSC Consideration

Palbociclib was anticipated to substitute for the existing listing of ribociclib. The actual utilisation was significantly greater in its first two years of listing than expected. In Year 2 the number of scripts dispensed was 17,398 compared to the forecast of [REDACTED] scripts.

- Uptake of palbociclib was substantially higher than estimated. It had the highest expenditure of all listings, based on the list price.
- Expenditure on protein kinase modulators has significantly increased since ribociclib and palbociclib were listed on the PBS.
- Expenditure on hormone modulating medicines (anastrozole, letrozole, exemestane, tamoxifen and fulvestrant) had remained stable since 2017 mainly from price reductions. But listing of fulvestrant in 2020 may increase expenditure in this group in the future.
- Expenditure on chemotherapy and immunotherapy listings has been declining since 2017, largely from price reductions applied to trastuzumab.

Actions undertaken by the DUSC Secretariat

The report was provided to the PBAC for comment.

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 sponsor has 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: Summary of price reductions that have been applied to breast cancer PBS listings

Drug name	Summary of price changes
Anastrozole	Statutory price reduction from 1 April 2012 Price disclosure reduction from 1 October 2014 Price disclosure reduction from 1 April 2015 Price disclosure reduction from 1 October 2015 Price disclosure reduction from 1 April 2016 Price disclosure reduction from 1 October 2016 Price disclosure reduction from 1 April 2017 Price disclosure reduction from 1 October 2017 Price disclosure reduction from 1 April 2021
Eribulin	5 year anniversary statutory price reduction, 1 April 2020
Everolimus	5 year anniversary statutory price reduction, 1 April 2016 10 year anniversary statutory price reduction, 1 April 2018 (certain listings) Statutory price reduction from 1 June 2028
Exemestane	Statutory price reduction from 1 August 2011 Price disclosure reduction from 1 April 2015 Price disclosure reduction from 1 April 2016 Price disclosure reduction from 1 October 2016 Price disclosure reduction from 1 April 2017
Fulvestrant	Statutory price reduction from 1 December 2021
Lapatinib	5 year anniversary statutory price reduction, 1 April 2016 10 year anniversary statutory price reduction, 1 April 2018 (certain listings)
Letrozole	Statutory price reduction from 1 April 2012 Price disclosure reduction from 1 October 2014 Price disclosure reduction from 1 April 2015 Price disclosure reduction from 1 October 2015 Price disclosure reduction from 1 October 2016 Price disclosure reduction from 1 October 2017
Nanoparticle albumin-bound paclitaxel	5 year anniversary statutory price reduction, 1 April 2016 10 year anniversary statutory price reduction, 1 April 2020
Pertuzumab	5 year anniversary statutory price reduction, 1 April 2021
Tamoxifen	Price disclosure reduction from 1 April 2015 Price disclosure reduction from 1 October 2016 Price disclosure reduction from 1 October 2017

Drug name	Summary of price changes
Trastuzumab	5 year anniversary statutory price reduction, 1 April 2016 10 year anniversary statutory price reduction, 1 April 2018 (certain listings) Statutory price reduction from 1 August 2019 Price disclosure reduction from 1 October 2020
Trastuzumab emtansine	5 year anniversary statutory price reduction, 1 April 2021
Vinorelbine	Price disclosure reduction from 1 April 2015 Price disclosure reduction from 1 October 2015

Sources:

Five year anniversary price reductions: <https://www.pbs.gov.au/info/industry/pricing/anniversary-price-reductions/5-year-anniversary>

Ten year anniversary price reductions: <https://www.pbs.gov.au/info/industry/pricing/anniversary-price-reductions/10-year-anniversary>

Fifteen year anniversary price reductions: <https://www.pbs.gov.au/info/industry/pricing/anniversary-price-reductions/15-year-anniversary>

Price disclosure outcomes: <https://www.pbs.gov.au/info/industry/pricing/price-disclosure-spd#Outcomes>

First new brand price reductions: <https://www.pbs.gov.au/info/industry/pricing/pbs-items/first-new-brand-price-reductions>