

Antifungals for systemic use

Drug utilisation sub-committee (DUSC)

September 2016

Abstract

Purpose

The analysis examined the utilisation of antifungal medicines for systemic use. This includes a predicted versus actual analysis of the voriconazole listing for prophylaxis against invasive fungal infections in certain high risk patients.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

The systemic antifungal medicines currently listed on the PBS are: fluconazole, itraconazole, posaconazole, voriconazole, terbinafine and griseofulvin. There have been a number of changes to the PBS listings for systemic antifungals since the last DUSC analysis in October 2013. Ketoconazole was removed from the Australian market in December 2013. Voriconazole was listed for prophylaxis against invasive fungal infections in December 2014. Posaconazole tablets were listed on 1 September 2015. Fluconazole and itraconazole became Restricted Benefit listings in April 2016.

Data Source / methodology

The analyses use data from the DUSC database, the Department of Human Services (DHS) Medicare Supplied prescriptions database and the DHS Authority approvals database from January 2008 to July 2016. Telephone and streamlined authority medicines were matched to their authority approvals to identify the restriction for use.

Key Findings

- In the 2015-16 financial year, 91,874 people received systemic antifungal medicines on the R/PBS. There were 203,228 prescriptions supplied at cost of \$35,564,069 to the R/PBS.
- Terbinafine and griseofulvin were the most widely used medicines with over 30,000 people supplied each of the medicines in the 2015 16 financial year.
- Terbinafine had remained the most utilised antifungal in terms of the prescriptions supplied since 2008. The number of fluconazole, itraconazole and posaconazole prescriptions had continued to increase. The number of voriconazole prescriptions had decreased after peaking in 2012. The number of griseofulvin prescriptions had remained relatively stable since 2012.
- Posaconazole had the highest PBS expenditure, costing \$18,347,465 in the 2015-16 financial year.

- There had been a sharp increase in the use of fluconazole since it changed to a Restricted Benefit from 1 April 2016. This may have been due to use for vulvovaginal candidiasis and dermatophyte infections.

Purpose of analysis

The analysis examined the utilisation of antifungal medicines for systemic use. This includes a predicted versus actual analysis of the voriconazole listing for prophylaxis against invasive fungal infections in certain high risk patients.

Background

Pharmacology

Fluconazole, posaconazole and voriconazole are triazole antifungals. They inhibit the enzyme lanosterol 14 α -demethylase. This is thought to damage the fungal membrane and cause a build-up of methylated precursors. This results in the inhibition of cell growth and/or cell death.¹

Terbinafine inhibits the fungal enzyme squalene epoxidase which is involved in ergosterol synthesis. This results in an ergosterol deficiency and accumulation of squalene, resulting in fungal cell death.²

Therapeutic Goods Administration (TGA) approved indications

Fluconazole is indicated for the following conditions³:

- Cryptococcal meningitis in patients who are unable to tolerate amphotericin B,
- Prevention of cryptococcal meningitis relapse in patients with acquired immune deficiency syndrome (AIDS),
- Treatment of oropharyngeal and oesophageal candidiasis in immunosuppressed patients,
- Secondary prophylaxis of oropharyngeal candidiasis in patients with HIV infection,
- Serious and life-threatening *Candida* infections in patients who are unable to tolerate amphotericin B,
- Vaginal candidiasis, when topical therapy has failed, and,
- Treatment of extensive tinea corporis, extensive tinea cruris and extensive tinea pedis infections in immunocompetent patients in whom topical therapy is not a practical treatment option.

Itraconazole is indicated in adults for the treatment of⁴:

- Superficial dermatomycoses not responding to topical treatment,
- Fungal keratitis that is rapidly spreading, immediately sight threatening or has failed to respond to topical treatment,
- Pityriasis versicolor not responding to any other treatment,
- Vulvovaginal candidiasis not responding to topical treatment,
- Oral candidiasis in immunocompromised patients,
- Onychomycosis (fungal infection of the nail) caused by dermatophytes,
- Systemic aspergillosis, histoplasmosis and sporotrichosis,

- Treatment and maintenance therapy of disseminated or chronic pulmonary histoplasmosis infection in patients with AIDS,
- Treatment of oropharyngeal and/or oesophageal candidiasis when first line systemic antifungal therapy is inappropriate or has proven ineffective, and,
- Treatment of non-invasive candidiasis in non-neutropenic patients when first-line systemic antifungal therapy is inappropriate or has proven ineffective. This may be due to underlying pathology, insensitivity of the pathogen or drug toxicity.

Posaconazole is indicated for the following conditions¹:

- Invasive aspergillosis in patients intolerant of, or with disease that is refractory to, alternative therapy.
- Fusariosis, zygomycosis, coccidioidomycosis, chromoblastomycosis, and mycetoma in patients intolerant of, or with disease that is refractory to, alternative therapy.
- Treatment of oropharyngeal candidiasis in immunocompromised adults, including patients with disease that is refractory to itraconazole and fluconazole. Only the oral suspension should be used for this indication.
- Prophylaxis of invasive fungal infections among patients 13 years of age and older, who are at high risk of developing these infections, such as patients with prolonged neutropenia or haematopoietic stem cell transplant (HSCT) recipients.

Voriconazole is indicated for⁵:

- Invasive aspergillosis,
- Serious Candida infections,
- Serious fungal infections caused by *Scedosporium* and *Fusarium* species,
- Other serious fungal infections, in patients intolerant of, or refractory to, other therapy, and,
- Prophylaxis in patients who are at high risk of developing invasive fungal infections (based on patients undergoing HSCT).

Terbinafine is indicated for²:

- Treatment of ringworm due to infection caused by dermatophytes such as trichophyton where oral therapy is appropriate due to site, severity or extent of the infection, and the infection is not responsive to topical therapy, and,
- Onychomycosis in adults caused by dermatophyte fungi.

Griseofulvin is indicated for the treatment of fungal infections of the skin, scalp, hair or nails, where topical therapy is considered inappropriate or has failed.⁶

Ketoconazole was deregistered and its supply discontinued in Australia on 1 December 2013 due to risk of liver injury.⁷ It was indicated for systemic and deep mycoses and recalcitrant cases of superficial mycoses.⁸ Ketoconazole is marketed in the United States (US) for certain fungal infections for patients who are unable to take or have failed other therapies. In July 2013, the US Food and Drug Administration (FDA) made a safety announcement on the risks of liver injury, adrenal gland problems and drug interactions with the use of oral ketoconazole.⁹

Dosage and administration

Dosage and administration information are presented in Appendix 1.

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 1 August 2016)

Table 1 presents the PBS listing of systemic antifungal medicines at 1 August 2016. All systemic antifungals listed on the PBS are listed in the General Schedule (section 85).

Table 1: PBS listing of systemic antifungals

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ \$	Brand name [manufacturer]
1471K	fluconazole 50 mg capsule, 28	28	5	25.09	Numerous brands
1472L	fluconazole 100 mg capsule, 28	28	5	38.84	Numerous brands
1473M	fluconazole 100 mg/50 mL injection, 50 mL vial	7	0	21.79	Numerous brands
1474N	fluconazole 200 mg/100 mL injection, 100 mL vial	7	0	31.73	Numerous brands
1475P	fluconazole 200 mg capsule, 28	28	5	65.64	Numerous brands
1757L	fluconazole 400 mg/200 mL injection, 200 mL bag	1	0	15.31	Fluconazole Alphapharm [Alphapharm Pty Ltd]
5446P	fluconazole 50 mg/5 mL oral liquid: powder for, 35 mL	1	0	66.75	Diflucan [Pfizer Australia Pty Ltd]
10732W	itraconazole 50 mg capsule, 60	60	5	150.53	Lozanoc [Mayne Pharma International Pty Ltd]
8196J	itraconazole 100 mg capsule, 60	60	5	222.91	Sporanox [Janssen-Cilag Pty Ltd]
10460M	posaconazole 100 mg tablet: modified release, 24	24	0	834.12	Noxafil [Merck Sharp & Dohme (Australia Pty Ltd)]
9360P	posaconazole 40 mg/mL oral liquid, 105 mL	1	0	691.44	Noxafil [Merck Sharp & Dohme (Australia Pty Ltd)]
10168E	voriconazole 40 mg/mL oral liquid: powder for, 70 mL	1	0	495.60	Vfend [Pfizer Australia Pty Ltd]
10173K	voriconazole 50 mg tablet, 56	56	0	492.95	Numerous brands
10198R	voriconazole 200 mg tablet, 56	56	0	1,894.70	Numerous brands

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ \$	Brand name [manufacturer]
9363T	voriconazole 50 mg tablet, 56	56	2	492.95	Numerous brands
9364W	voriconazole 200 mg tablet, 56	56	2	1,894.70	Numerous brands
9452L	voriconazole 40 mg/mL oral liquid: powder for, 70 mL	1	0	495.6	Vfend [Pfizer Australia Pty Ltd]
1460W	griseofulvin 125 mg tablet, 100	100	2	26.62	Grisovin [Aspen Pharma Pty Ltd]
2982Y	griseofulvin 500 mg tablet, 28	28	2	27.56	Grisovin 500 [Aspen Pharma Pty Ltd]
2285G ^a	terbinafine 250 mg tablet, 42	42	0	34.34	Numerous brands
2804N ^b	terbinafine 250 mg tablet, 42	42	1	34.34	Numerous brands
4011D (RPBS)	terbinafine 250 mg tablet, 42	42	1	34.34	Numerous brands

Source: the [PBS website](#).

^a Dermatophyte infection in Aboriginal or a Torres Strait Islander person or a person aged up to 18 years after other treatments have failed.

^b Proximal or extensive onychomycosis where topical treatment has failed.

Restriction

Fluconazole capsules and injections have Restricted Benefit listings for the following conditions:

- Cryptococcal meningitis,
- Maintenance therapy of cryptococcal meningitis for immunosuppressed patients,
- Oropharyngeal candidiasis in immunosuppressed patients,
- Oesophageal candidiasis in immunosuppressed patients,
- Prophylaxis of oropharyngeal candidiasis in immunosuppressed patients, and,
- Serious or life-threatening candida infections.

Fluconazole suspension has a Restricted Benefit listing for the same conditions as the capsule and injection listings but require that patients are unable to take the solid dose form of fluconazole.

Itraconazole has a Restricted Benefit listing for:

- Systemic aspergillosis,
- Systemic sporotrichosis,
- Systemic histoplasmosis,
- Treatment and maintenance therapy of disseminated pulmonary histoplasmosis infection of patients with AIDS,

- Treatment and maintenance therapy of chronic pulmonary histoplasmosis infection of patients with AIDS,
- Oropharyngeal candidiasis in immunosuppressed patients, and,
- Oesophageal candidiasis in immunosuppressed patients.

Posaconazole has an Authority Required (telephone authority) listing for the treatment of the following fungal infections for patients unable to tolerate alternative therapy or the condition is refractory to alternative therapy:

- Invasive aspergillosis,
- Fusariosis,
- Zygomycosis,
- Coccidioidomycosis,
- Chromoblastomycosis, and,
- Mycetoma.

It is also listed for prophylaxis against invasive fungal infections in the following high risk populations:

- Patients receiving chemotherapy for acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) where neutropenia absolute neutrophil count less than 500 cells/cm³ is expected for at least 10 days; and,
- Patients with acute graft versus host disease (GVHD) grade II, III or IV, or extensive chronic GVHD, and receiving intensive immunosuppressive therapy after allogeneic haematopoietic stem cell transplant.

Voriconazole has an Authority Required (telephone authority) listing for the treatment and maintenance therapy of the following conditions:

- Definite or probable aspergillosis in patients who are immunocompromised,
- Serious fungal infections caused by *Scedosporium* or *Fusarium* species,
- Serious *Candida* infections that are not susceptible or resistant to fluconazole or for patients unable to tolerate fluconazole, and,
- Serious invasive mycosis infections (not aspergillosis).

Voriconazole also has an Authority Required listing for prophylaxis against invasive fungal infections for the following high risk patient groups:

- Patients receiving chemotherapy for AML or MDS where neutropenia absolute neutrophil count less than 500 cells/cm³ is expected for at least 10 days,
- Patients with acute graft versus host disease (GVHD) grade II, III or IV, or extensive chronic GVHD, and receiving intensive immunosuppressive therapy after allogeneic haematopoietic stem cell transplant, and,
- Patients undergoing allogeneic haematopoietic stem cell transplant using either bone marrow from an unrelated donor or umbilical cord blood (related or unrelated), and, are considered to be at high risk of developing an invasive fungal infection during the neutropenic phase prior to engraftment.

Terbinafine has Authority Required listings for the treatment of dermatophyte infection in the following groups:

- Aboriginal or a Torres Strait Islander person where topical treatment has failed;
- Patient aged up to 18 years, inclusive where topical treatment and griseofulvin have failed; and
- Proximal or extensive (greater than 80% nail involvement) onychomycosis due to dermatophyte infection where topical treatment has failed.

Griseofulvin has an unrestricted listing.

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

Date of listing on PBS

Changes to listing

On 1 January 2011, fluconazole, itraconazole and ketoconazole became streamlined authority listings.

Ketoconazole was delisted from the PBS and removed from the Australian market on 1 December 2013.

Voriconazole was listed for prophylaxis against invasive fungal infections on 1 December 2014. It was listed for the high risk groups eligible for posaconazole under its prophylaxis listing as well as certain high risk patients undergoing haematopoietic allogeneic stem cell transplantation (AlloHSCT).

Posaconazole tablets were listed on 1 September 2015 for the same restrictions as the oral liquid.

In April 2016, the listings for fluconazole and itraconazole were changed from streamlined authority listings to Restricted Benefit listings. The wording of the restrictions was not changed. The fluconazole suspension listing was changed from a telephone Authority listing to a Restricted Benefit listing.

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

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

Voriconazole for prophylaxis

At its March 2014 meeting, the PBAC recommended listing voriconazole for prophylaxis against invasive fungal infection in high risk patients groups with AML, MDS, GVHD and high risk AlloHSCT recipients. The recommendation was made on a cost minimisation basis against a weighted mixed comparator of posaconazole, fluconazole and itraconazole in the GVHD and AlloHSCT high risk patient populations. In the AML/MDS high risk patient

population, the PBAC recommended listing voriconazole on a cost-minimisation basis compared to only fluconazole and itraconazole.

The PBAC noted that the market share of voriconazole for the existing population (AML, MDS and GVHD) could possibly be greater than the 30% proposed in the submission as voriconazole does not require administration with a fatty meal, can be used in younger children and may be an easier formulation to administer. However, this would take market from posaconazole. The PBAC considered that the number of true high risk AlloHSCT patients may be overestimated. It is also possible that a proportion of the medium risk AlloHSCT population will access treatment and this is use beyond the restriction. There is scope for growth of the overall market of eligible patients as posaconazole may be more difficult to use and there are advantages for voriconazole. This is likely to be small and may represent cost shifting from hospital budgets to Commonwealth budgets. The PBAC recommended a risk sharing agreement between the sponsor and Commonwealth be entered into to limit utilisation in low risk patient populations and for indications other than prophylaxis.

For further details refer to the [Public Summary Document](#) from the March 2014 PBAC meeting.

Posaconazole tablets

At its March 2015 meeting, the PBAC recommended the listing of posaconazole tablets for the same treatment and prophylaxis restrictions as the oral liquid. The PBAC noted that there is no conclusive data to support a clinical decision to discontinue treatment or discontinue prophylaxis in chronic graft-versus-host disease. The PBAC considered that there is a risk that patients will persist on treatment in the absence of clear additional clinical benefit.

The PBAC considered that utilisation of posaconazole tablets should be reviewed by DUSC after listing, noting that usage is likely to increase due to ease of use of tablets over liquid. The Committee considered that it is uncertain whether any additional patient benefit from such increased use will accrue. In the context of a DUSC analysis, the PBAC considered it appropriate to consult experts responsible for the current antifungal treatment guidelines to ascertain the most appropriate duration of therapy for both prophylaxis and treatment in order to form a basis for accurately analysing usage.

For further details refer to the [Public Summary Document](#) from the March 2015 PBAC meeting.

Post-market review of authority required PBS listings

Systemic antifungal medicines were considered by the PBAC at its August 2015 meeting. The PBAC considered fluconazole and itraconazole to no longer meet the criteria for an Authority Required listing and recommended they be changed to Restricted Benefit listings. The PBAC considered voriconazole, posaconazole and terbinafine remain telephone authority medicines because there is a risk of use in populations in which cost-effectiveness had not been assessed.

Approach taken to estimate utilisation

Voriconazole for prophylaxis

The submission used the following steps to estimate utilisation in the high risk allogenic HSCT population:

- The number of allogenic HSCTs performed in Australia in 2009 from the Australian Bone Marrow Transplant Registry Report.
- It was assumed that the number of transplants would grow at the same rate as the Australian population using Australian Bureau of Statistics data. This was 1.5% per year from 2009 to 2012-13 and 1.4% per year thereafter.
- 50% of allogenic HSCTs use an unrelated donor. It was assumed all patients receive antifungal prophylaxis.
- Using a clinician survey it was estimated 39% of patients use posaconazole, 22% use voriconazole and 39% use other antifungals such as fluconazole and itraconazole.
- Voriconazole market share would increase to 44% in the first year of listing, 54% in the second year of listing and 60% for the third to fifth years of listing.
- It was estimated 3% of allogenic HSCTs will be performed in private hospital using AR-DRG data. Private hospital inpatients will receive one IV voriconazole loading dose, 4 days of continuing IV voriconazole and 28 days of inpatient oral voriconazole (one prescription). It was estimated that patients will receive 63 days of voriconazole treatment after hospital (three prescriptions).

The submission used a market share approach for the neutropenia and GVHD patient groups. It made the following steps to estimate utilisation:

- Extracted the number of posaconazole prescriptions supplied in the 2012-13 financial year from Medicare services data. The submission estimated prescriptions supplied would increase 18% to 2013-14, then 12% to 2014-15 (first year of listing), 7% in 2015-16 and 5% for each year thereafter.
- Based on the previous DUSC analysis, it was estimated 75% of posaconazole prescriptions were for prophylaxis and there were an average of four packs per prescription.
- It was estimated four packs of posaconazole would provide 28 days treatment.
- Using a clinician survey, it was estimated posaconazole accounted for 45% of the prophylaxis market. Voriconazole was estimated to have 18% and other antifungals 36%. This was used to estimate the total number of months of prophylaxis used each year.
- It was assumed that the voriconazole market share would increase to █ in the first year of listing, █ in the second year and █ from the third year onwards. It was assumed █ would be from existing posaconazole market and █ from other antifungals. It was assumed posaconazole's market share will decline to █ in the first year of listing to █ in the third to fifth years of voriconazole's listing.
- The submission did not estimate the number of patients that would be treated.

A summary of the estimates are presented in Table 2.

Table 2: Voriconazole estimates for prophylaxis

	Year 1	Year 2	Year 3	Year 4	Year 5
High risk allogenic HSCT patients					
High risk allogenic HSCTs	224	228	231	235	238
Patients prescribed voriconazole	■	■	■	■	■
Prescriptions	■	■	■	■	■
Neutropenia and GVHD patients					
PBS posaconazole services (prescriptions)	4,735	5,067	5,321	5,588	5,868
Posaconazole treatment months	3,551	3,800	3,991	4,191	4,401
Voriconazole prescriptions for prophylaxis	■	■	■	■	■
Total voriconazole prophylaxis prescriptions	■	■	■	■	■
Total cost (DPMQ)	\$5,236,308	\$6,422,840	\$7,356,919	\$7,693,523	\$8,046,959
Patient co-payments	\$35,766	\$43,870	\$50,250	\$52,549	\$54,963
Net cost to government	\$5,200,543	\$6,378,970	\$7,306,669	\$7,640,974	\$7,991,995

Source: Voriconazole submission

Previous reviews by the DUSC

DUSC previously reviewed the utilisation of systemic antifungal medicines at its October 2013 meeting. It considered that the increasing utilisation of antifungal medicines reflected a larger number of immunosuppressed patients in the community; such as patients with cancer, haematopoietic and solid organ transplants, and cystic fibrosis. The committee noted the increasing prevalence of HIV would also be a contributing factor to higher antifungal utilisation. DUSC noted that there may be an increasing number of patients undergoing myelosuppressive chemotherapy regimens and bone marrow transplants, particularly in older age groups. The committee noted the removal of ketoconazole from the Australian market may have an impact on the utilisation of other antifungal medicines.

Methods

This analysis used data from the DUSC database, the Department of Human Services (DHS) Medicare Supplied prescriptions database and the DHS Authority approvals database. The DUSC database was used for the majority of analyses presenting aggregate prescription data. The DUSC database combines data on PBS prescriptions submitted to the Department of Human Services (DHS) for payment of a PBS/RPBS subsidy by the Government with an estimate of under patient co-payment prescriptions based on dispensing data from a sample of pharmacies to the end of August 2012. This was replaced by actual under patient co-payment prescription data from 1 April 2012. The DUSC database includes an estimate

of private prescriptions to the end of August 2012. This data was not included in the analyses.

The DHS Supplied prescriptions database is used for analyses presenting patient counts, authority indications, practitioner speciality, patient age and government expenditure. The data includes under co-payment prescriptions from 1 April 2012. Authority indications for streamlined authority prescriptions are extracted from this database. Prescribers prescribing streamlined authority medicines are required to write the four digit authority code on the prescription that corresponds to the indication for which it is being prescribed. The dispensing pharmacist is required to include the code on the claim for PBS dispensing. Until December 2011, pharmacists were not required to record streamlined codes at the time of dispensing. Since 1 July 2012, DHS-Medicare is able to reject pharmacy claims for reimbursement for Authority Required (STREAMLINED) medicines with an invalid streamlined authority code or without a streamlined authority code.

The Authority approvals database was used to extract authority approval restriction codes for authority required medicines and streamlined authority medicines where a larger quantity or more repeats are required than stated on the PBS listing. Telephone authority approvals have a restriction code recorded in the Authority approvals database. Prescribers requesting approval state the eligible authority restriction to the DHS officer making the approval. This is then recorded on the database.

Medicines with authority listings were matched to an authority restriction code. Where a streamlined authority code was listed on the supplied prescriptions database, this code was considered to be the authority restriction code. Where there was no streamlined authority code attached to a supplied prescription, the corresponding authority approval was sought in the Authority approvals database. Prescriptions were matched to an approval if the deidentified patient identification number (PIN) and item codes matched for both the approval and supplied prescription. The date of authority approval must be before the supply date for it to be assigned as the corresponding approval.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available Department of Human Services (DHS) Medicare date of processing data.¹ The publicly available DHS Medicare data only includes subsidised R/PBS prescriptions with prescriptions under the patient co-payment not included.

¹ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

Results

Analysis of drug utilisation

Overall utilisation

Table 3 presents the number of patients who were supplied an antifungal on the R/PBS by financial year.

Table 3: Patients supplied systemic antifungals on the R/PBS

Year	July 2012 - June 2013	July 2013 - Jun 2014	Jul 2014 - June 2015	July 2015 - June 2016
All systemic antifungals	117,989	100,410	88,672	91,874
Fluconazole	13,323	15,155	16,414	22,013
Griseofulvin	30,934	31,370	31,195	30,078
Itraconazole	1,757	1,963	2,137	2,586
Ketoconazole ^a	29,069	11,934	-	-
Posaconazole	1,148	1,170	1,304	1,801
Terbinafine	42,929	39,578	37,860	35,940
Voriconazole	1,426	1,629	1,581	1,414

Source: DHS Supplied Prescriptions database, extracted August 2016

^a Ketoconazole was removed from the R/PBS and Australian market in December 2013.

The number of patients supplied antifungals on the R/PBS decreased between the 2012-13 and 2014-15 financial years but has increased 3.6% in the 2015-16 year. The number of patients supplied fluconazole, itraconazole, and posaconazole has increased. The number of patients supplied terbinafine has decreased steadily over the four years. The number of patients receiving voriconazole increased until the 2013-14 financial year and has decreased thereafter. The number of patients supplied griseofulvin has been stable during this period. Figure 1 presents the number of prescriptions for systemic antifungal medicines supplied on the R/PBS.

Table 4 presents total systemic antifungal prescriptions supplied on the R/PBS by financial year.

Table 4: Prescriptions for systemic antifungals on the R/PBS

Year	July 2012 - June 2013	July 2013 - Jun 2014	Jul 2014 - June 2015	July 2015 - June 2016
All systemic antifungals	241,907	213,182	198,148	203,228

Source: DHS Supplied Prescriptions database, extracted August 2016

The number of systemic antifungal prescriptions supplied decreased between the 2012-13 and 2014-15 financial years but has increased in the 2015-16 financial year.

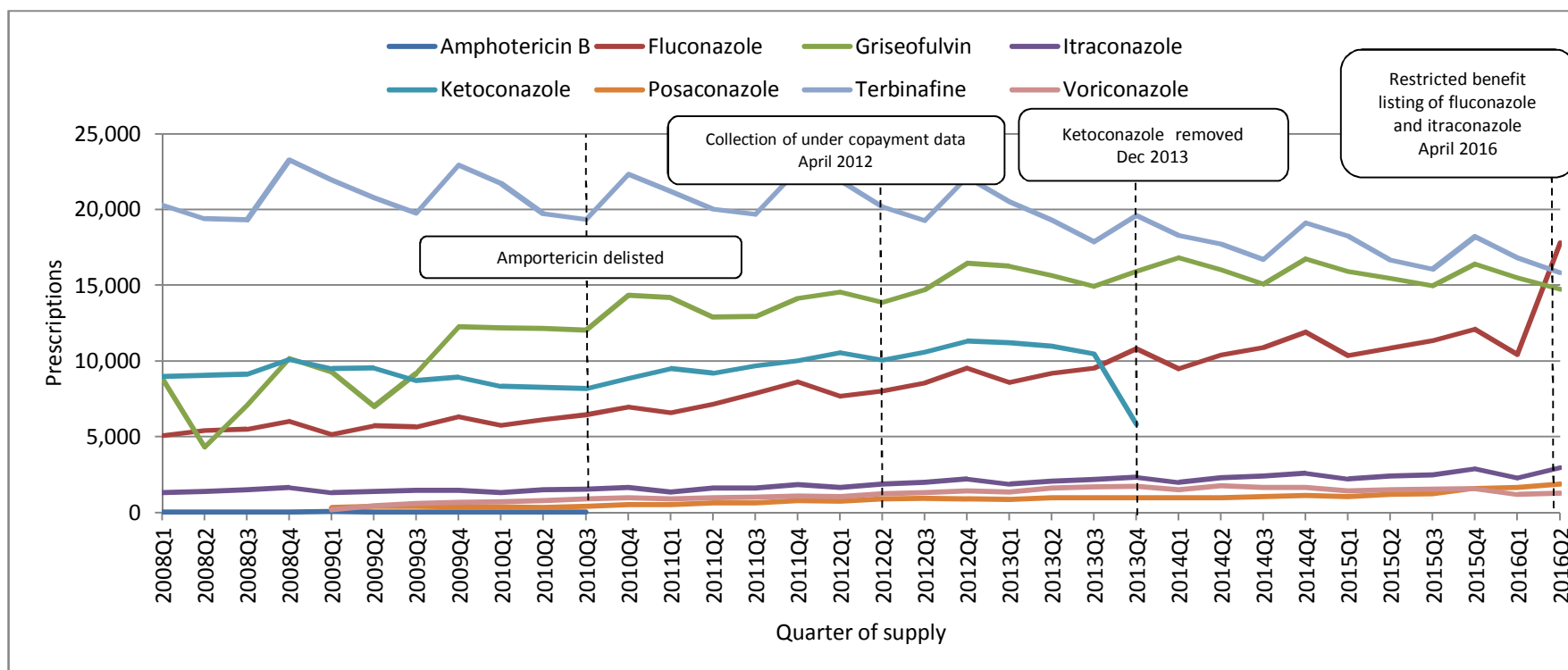


Figure 1: Utilisation of systemic antifungal medicines - prescriptions

Source: DUSC database, extracted August 2016

In the 2015-16 financial year, there were 203,228 prescriptions for systemic antifungals supplied on the R/PBS. Terbinafine has remained the most utilised antifungal in terms of the prescriptions supplied, with 67,001 prescriptions supplied in 2015-16. The number of terbinafine prescriptions supplied has decreased in 2012. The number of griseofulvin prescriptions supplied has remained relatively stable since 2012. The number of fluconazole, itraconazole and posaconazole prescriptions supplied has continued to increase. There is a sudden increase in fluconazole prescriptions in the second quarter of 2016 after the listing changed to a Restricted Benefit. The number of voriconazole prescriptions supplied has decreased after peaking in 2012.

Fluconazole

Figure 2 presents the number of fluconazole capsule prescriptions supplied on the R/PBS.

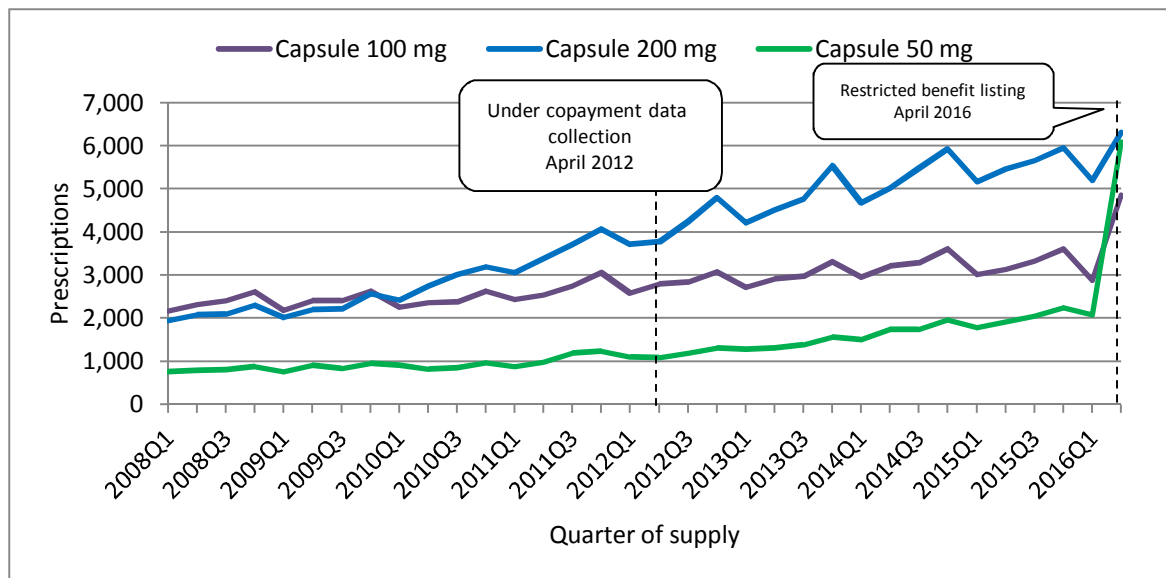


Figure 2: Fluconazole capsule prescriptions

Source: DUSC database, extracted August 2016.

The number of fluconazole capsule prescriptions supplied on the R/PBS has increased. The utilisation of all three strengths has increased but utilisation of the 200 mg capsules has increased more rapidly than the other strengths up to the first quarter of 2016. Utilisation of the 50 mg strength has rapidly increased three-fold in 2016. Utilisation of the 100 mg strength has also increased sharply but not to the same extent as the 50 mg strength.

Figure 3 presents the utilisation of fluconazole oral suspension and parenteral formulation.

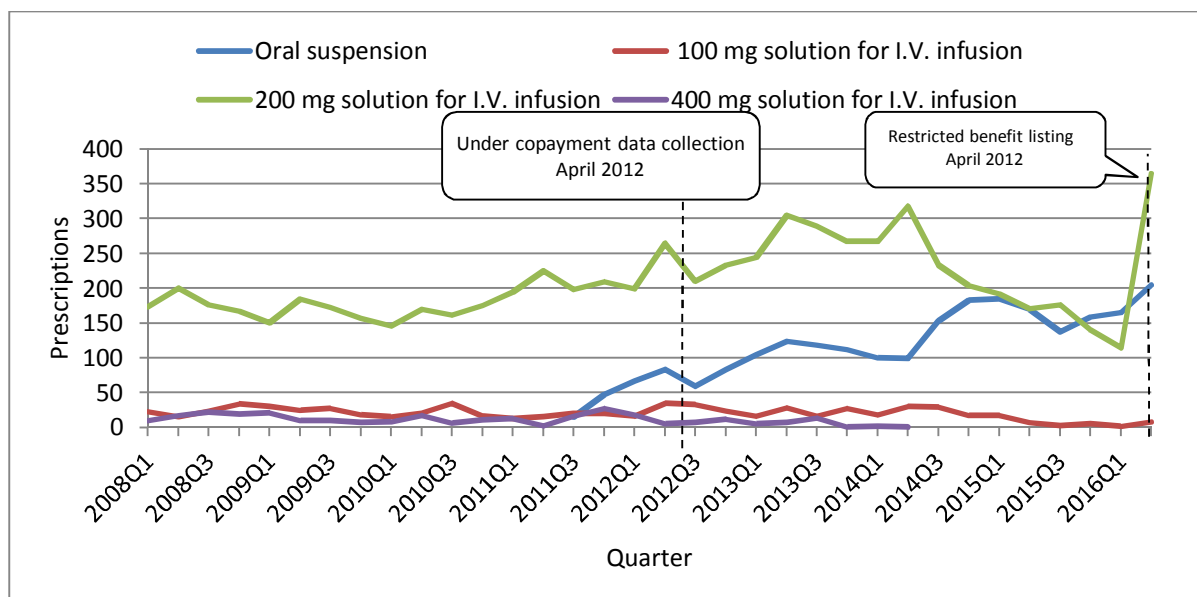


Figure 3: Fluconazole prescriptions for suspension and IV solution formulations

Source: DUSC database, extracted August 2016.

The utilisation of fluconazole products for IV administration decreased since 2014 to the second quarter of 2016 when utilisation of the 200 mg solution for IV infusion increased substantially. Data on quantity supplied confirmed an increase in utilisation of the 200 mg strength. The 400 mg solution of IV infusion is infrequently supplied on the R/PBS. The utilisation of the fluconazole suspension appears to have stabilised in 2014.

Figure 4 presents the authority restrictions for fluconazole prescriptions between 2008 and first quarter of 2016.

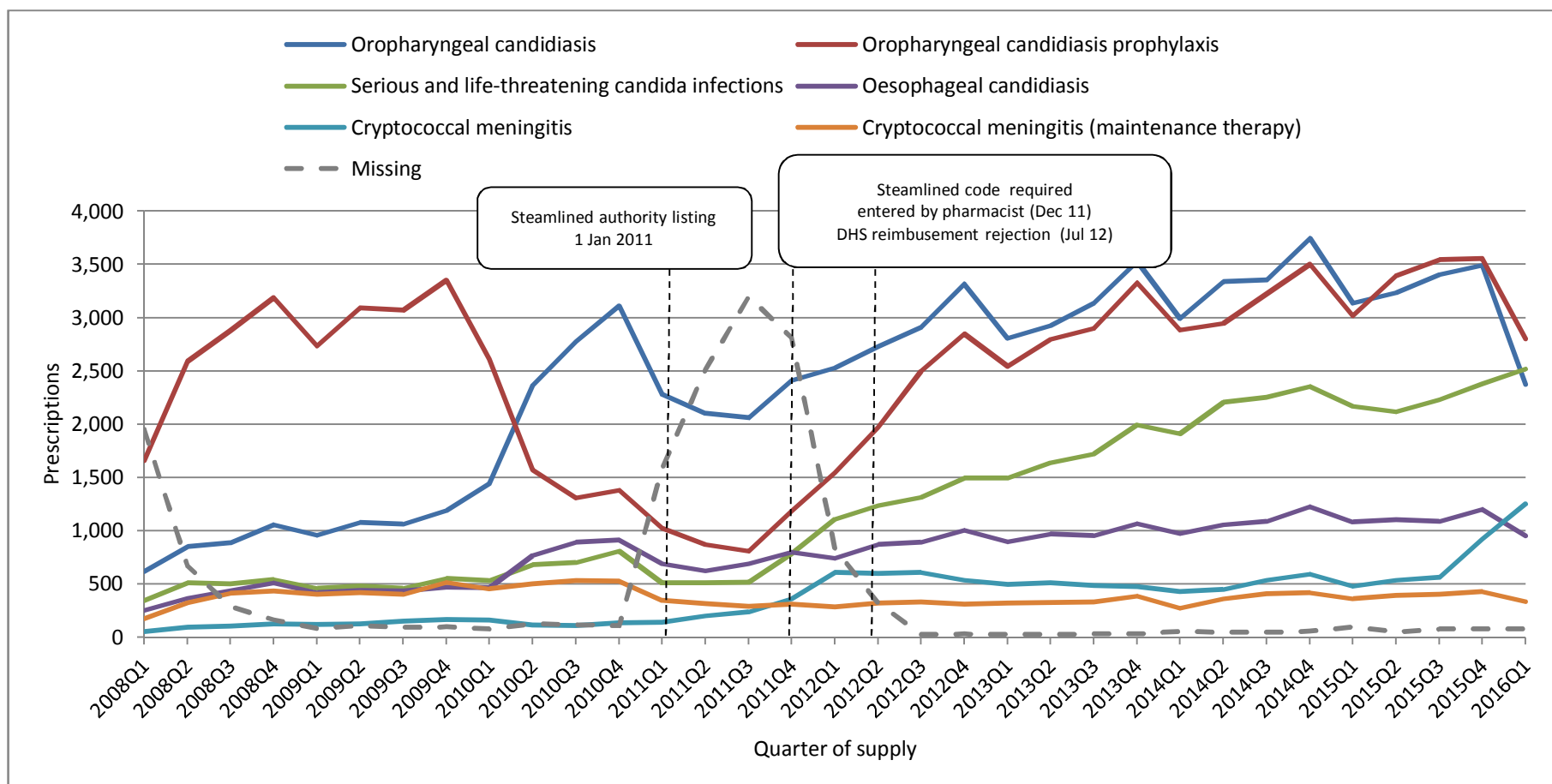


Figure 4: Fluconazole indications from authority codes – January 2008 to March 2016

Source: DHS supplied prescriptions database, DHS Authority approvals database, extracted July 2016.

Note: There were 168 prescriptions with special DVA authority approvals that are not included in the figure due to small number per quarter.

Treatment and prophylaxis against oropharyngeal candidiasis were the most common indications for fluconazole supply. Prescriptions for serious and life-threatening candida infections has increased five-fold from around 500 prescriptions per quarter to mid-2011 to 2,500 prescriptions per quarter in late 2015. There has also been an increase in number of prescriptions for treatment of cryptococcal

meningitis in late 2015. Following the introduction of the streamlined authority listing, there was a transient increase in in the number of prescriptions where an indication could not be matched. The proportion of prescriptions without an indication decreased to less than 1% of prescription in the third quarter of 2012. In 2015, 0.7% of prescriptions did not have an indication code. Since April 2016, fluconazole has had a Restricted Benefit listing. Restriction codes will only be captured for telephone authority prescriptions for higher quantities or repeats.

Due to the large increase in the number of fluconazole prescriptions supplied in the second quarter of 2016, analyses were undertaken to investigate possible reasons for the increase. Figure 5 presents the number of 50 mg and 100 mg capsule prescriptions by patient sex.

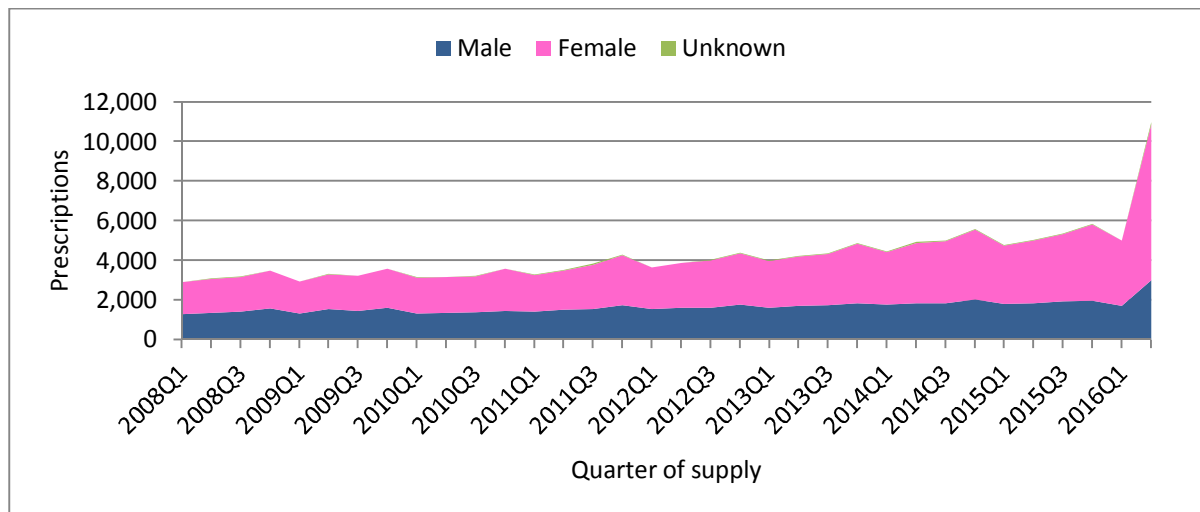


Figure 5: Fluconazole prescriptions for 50 mg and 100 mg capsules by sex

Source: DHS supplied prescriptions database, extracted August 2016.

A larger proportion of prescriptions supplied in the second quarter of 2016 were for female patients than earlier quarters. 72% of prescriptions were for females in the second quarter of 2016, compared to 64% of prescriptions in 2015.

Figure 6 compares the increase in fluconazole prescriptions for 50 mg or 100 mg capsules from the first to second quarters of 2016 compared to the corresponding period a year earlier by prescriber speciality.

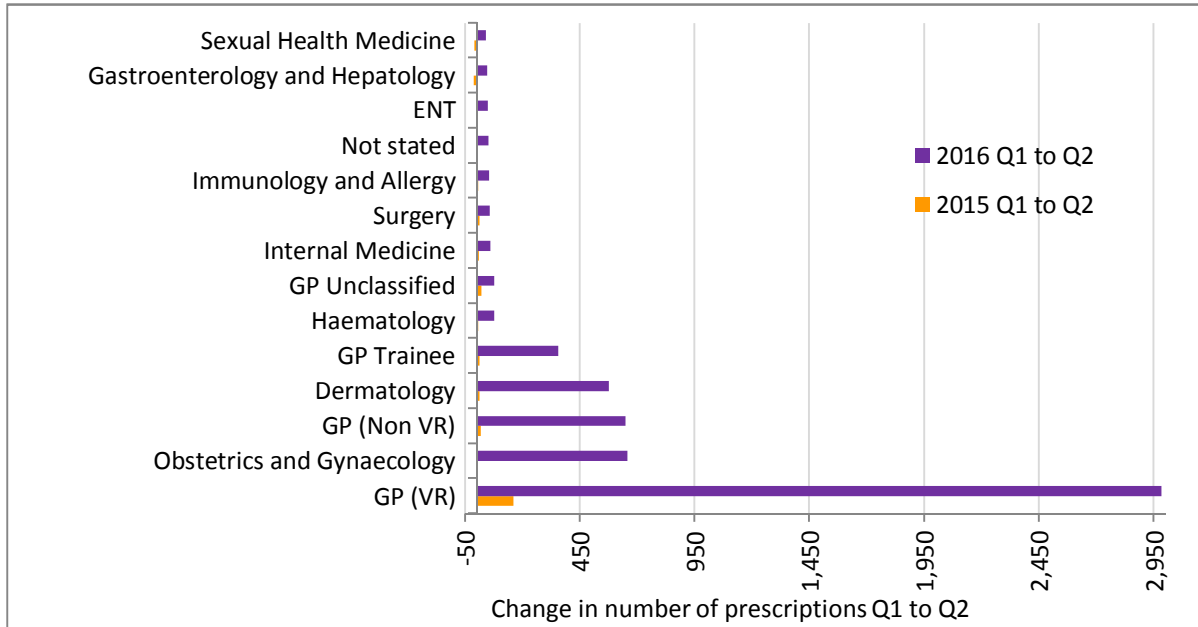


Figure 6: Changes in fluconazole prescribing by prescriber speciality – 50 mg and 200mg capsules

Source: DHS supplied prescriptions database, extracted August 2016.

Note: The graph only includes prescriber specialities with a large change in prescribing.

GP = general practitioner, VR = vocationally registered

The largest numerical increase in fluconazole prescriptions has been due to more prescriptions by general practitioners (all groups) followed by obstetricians and gynaecologists and dermatologists. Many of prescriber specialities listed on the figure have had large increases in fluconazole prescribing compared to the corresponding quarters in 2015.

Figure 7 presents the numerical increase in 200 mg fluconazole vial prescriptions by prescriber speciality from first to second quarter of 2016 compared to the corresponding quarter in 2016.

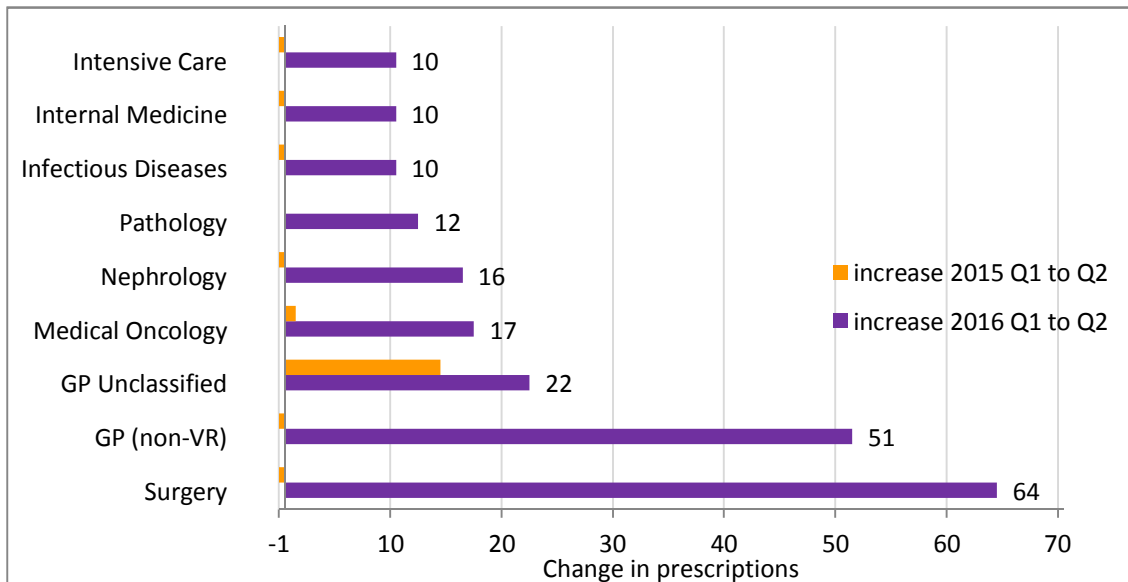


Figure 7: Changes in fluconazole prescribing by prescriber specialty – 200 mg IV

Source: DHS supplied prescriptions database, extracted August 2016.

Note: The graph only includes prescriber specialties with a large change in prescribing.

GP = general practitioner, VR = vocationally registered

Surgeons and non-vocationally registered general practitioners have had the largest increase in the number of 200 mg IV prescriptions supplied. There have also been smaller increases across a range of prescribers. The magnitude of the changes in prescribing that occurred from the first to second quarters of 2016 were larger than the changes that occurred in the corresponding period in 2015.

Figure 8 presents the number of repeats prescribed with each original fluconazole prescription.

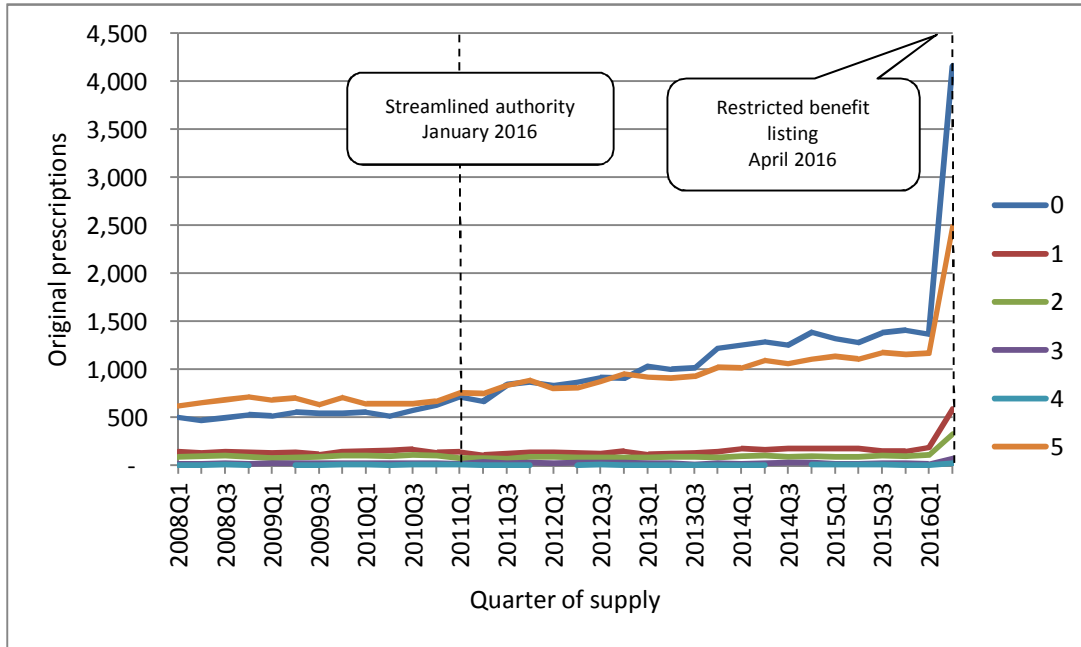


Figure 8: Fluconazole original prescriptions by repeats ordered – 50 mg and 200 mg capsules

Source: DHS supplied prescriptions database, extracted August 2016.

Note: Data excludes a small number of prescriptions with more than five repeats.

The number of original prescriptions with no repeats has increased over time to exceed the number of prescriptions with five repeats. The increase from 1 April 2016 in original prescriptions with no repeats in the second quarter of 2016 has been greater than other groups.

Itraconazole

Figure 9 presents the number of prescriptions for itraconazole capsules.

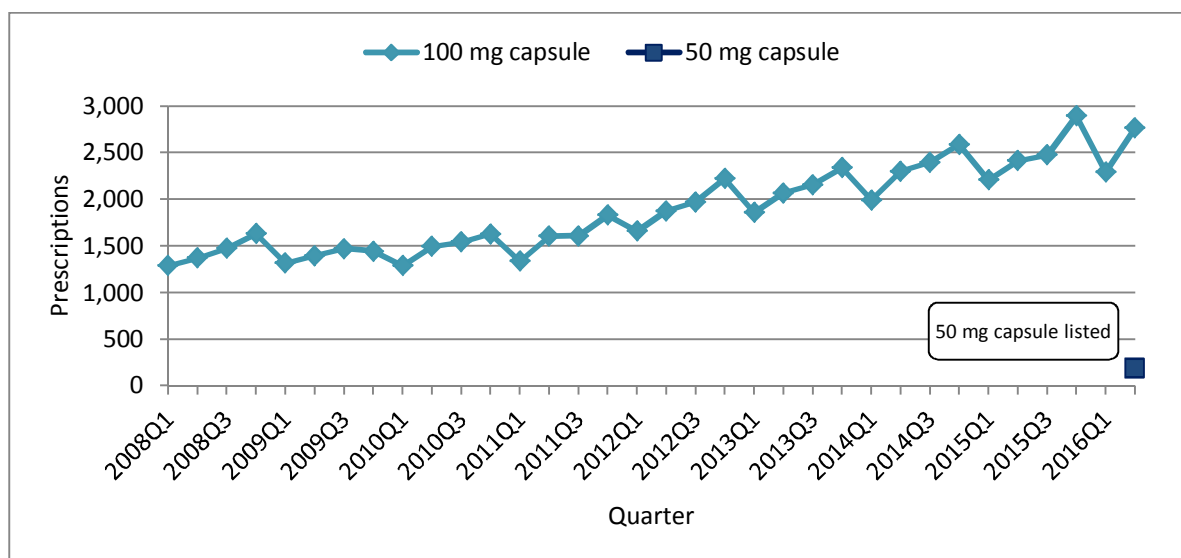


Figure 9: Itraconazole prescriptions

Source: DUSC database, extracted July 2016.

The number of itraconazole prescriptions supplied has increased steadily since 2011. Prior to 2011, the number of prescriptions supplied per quarter was relatively stable. There have been a small number of 50 mg capsules supplied since they were listed on 1 April 2016. The 50 mg Lozanoc brand capsules are therapeutically equivalent to the 100 mg Sporanox capsules.

Figure 10 presents itraconazole prescriptions by authority restriction codes.

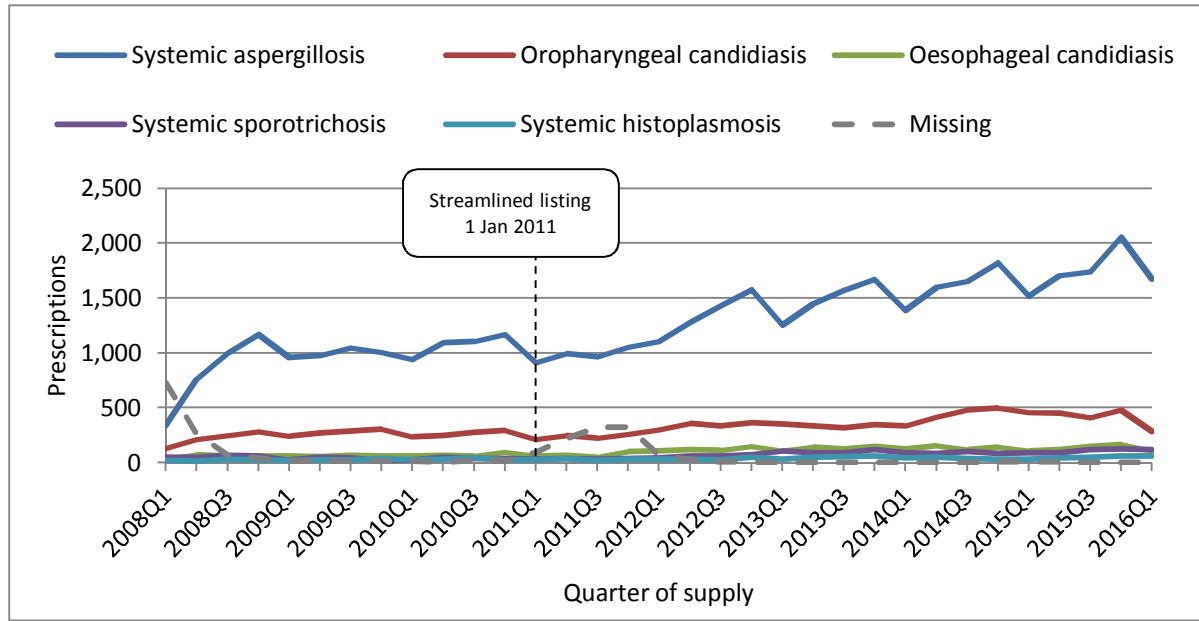


Figure 10: Itraconazole prescriptions by authority indication – January 2008 to March 2016

Source: DUSC database, DHS Authority approvals database, extracted July 2016.

Note: There were 130 prescriptions with special DVA authority approvals that are not included in the figure due to small number per quarter.

Systemic aspergillosis is the most common indication for itraconazole supply. The number of prescriptions supplied for this indication has almost doubled since 2011. The increase in utilisation for systemic aspergillosis appears to be responsible for most of the increase in itraconazole supply on the R/PBS. Since April 2016, itraconazole has had a Restricted Benefit listing. Restriction codes will only be captured for telephone authority prescriptions for higher quantities or repeats.

Posaconazole

Figure 11 presents the number of posaconazole prescriptions supplied on the R/PBS.

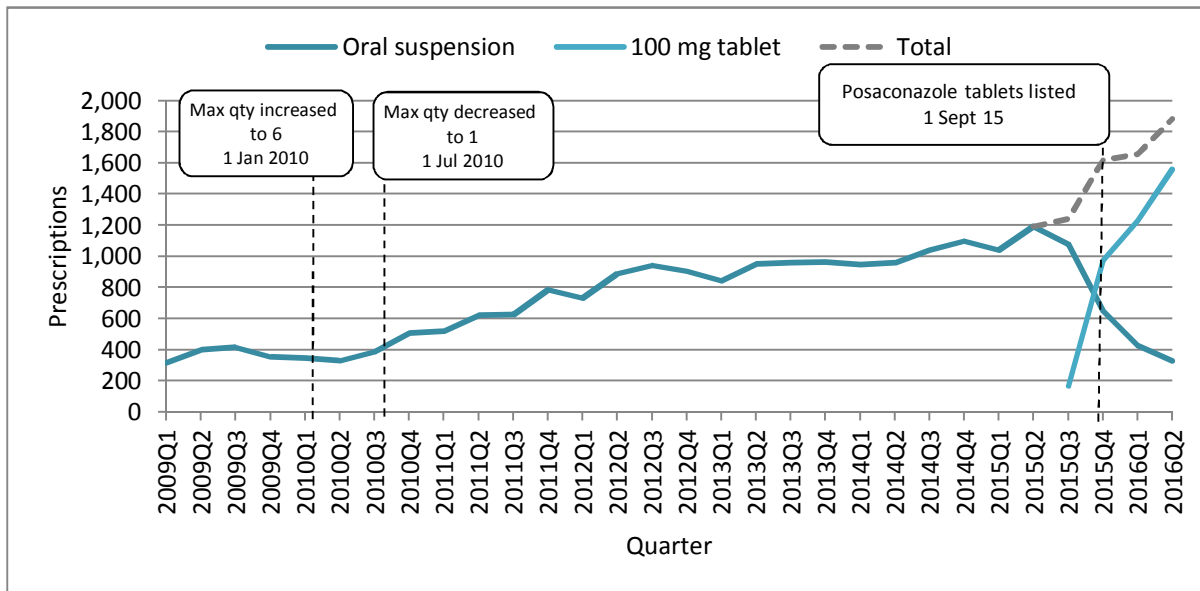


Figure 11: Posaconazole prescriptions

Source: DUSC database, extracted July 2016.

The number of posaconazole prescriptions supplied on the PBS has increased steadily since 2009. The number of prescriptions supplied somewhat plateaued from 2012 to 2014 before increasing in the second half of 2015 coinciding with the availability of the tablet form.

Figure 12 presents posaconazole prescription by authority restriction codes.

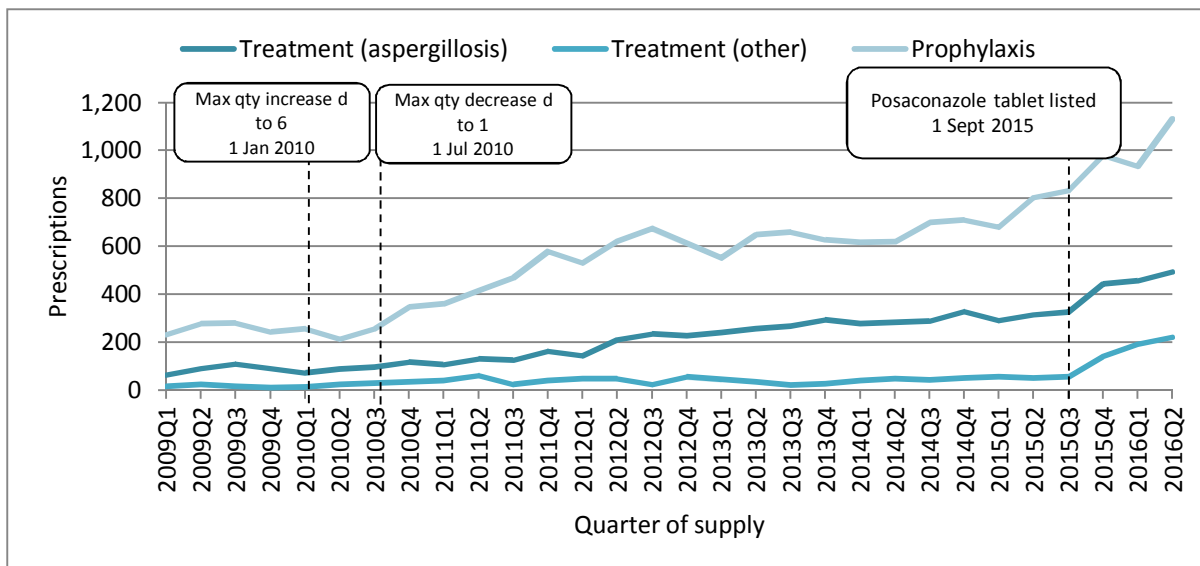


Figure 12: Posaconazole prescriptions by authority indication

Source: DHS supplied prescriptions database, DHS Authority approvals database, extracted July 2016.

Note: There were 17 prescriptions with special DVA authority approvals that are not included in the figure due to the small number per quarter. Approximately 1% of posaconazole prescriptions did not have an indication code and are not included in the above figure.

Note: Treatment (other) is for the treatment of the following fungal infections fusariosis, zygomycosis, coccidioidomycosis, chromoblastomycosis or mycetoma.

Prophylaxis against invasive fungal infections remains the most common indication for the posaconazole supply. The number of prescriptions supplied for prophylaxis was relatively stable between 2012 and 2014. The number of prescriptions for the treatment of aspergillosis steadily increased while prescriptions for the treatment of other fungal infections were low and variable. The number of prescriptions for prophylaxis began to increase in mid-2015. The number of prescriptions for both treatment authority codes increased in late 2015, around the time of listing of the tablet formulation. There was a decrease in the number of prescriptions for prophylaxis in the first quarter of 2016 that is not seen for the treatment indications. This may be due to patients using prophylaxis who have reached the PBS safety net having more prescriptions dispensed at the end of the year. This seasonal supply pattern would be much less likely in patients diagnosed with a fungal infection.

Figure 13 presents the number of posaconazole doses that were supplied on the R/PBS for prophylaxis. Posaconazole suspension is administered at a dose of 200 mg three times daily for prophylaxis (600 mg daily). Posaconazole tablets are used at a dose of 300 mg daily for prophylaxis. Only prescriptions matched to an authority approval for prophylaxis are included.

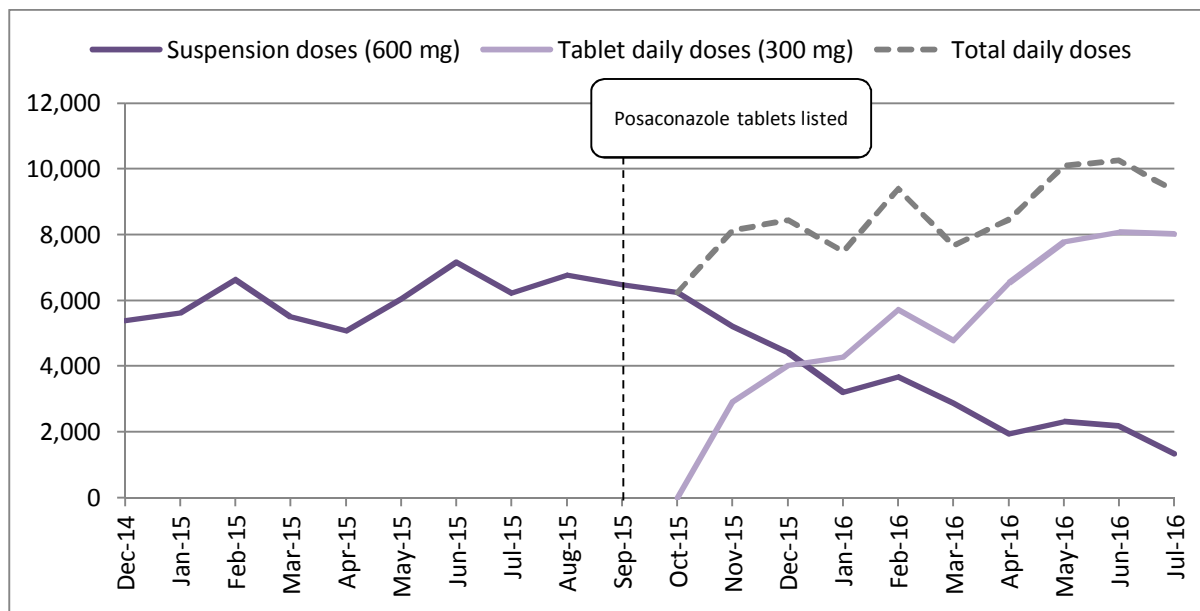


Figure 13: Posaconazole doses for prophylaxis

Source: DHS supplied prescriptions database, extracted August 2016

The number of posaconazole doses supplied on the PBS for prophylaxis has increased since the listing of the tablet formulation. Before the tablet listing, the number of prophylaxis doses appears to be increasing slowly. The number of daily doses supplied increased at a faster rate following the listing of the tablets.

Voriconazole

Figure 14 presents prescriptions for voriconazole by dosage form.

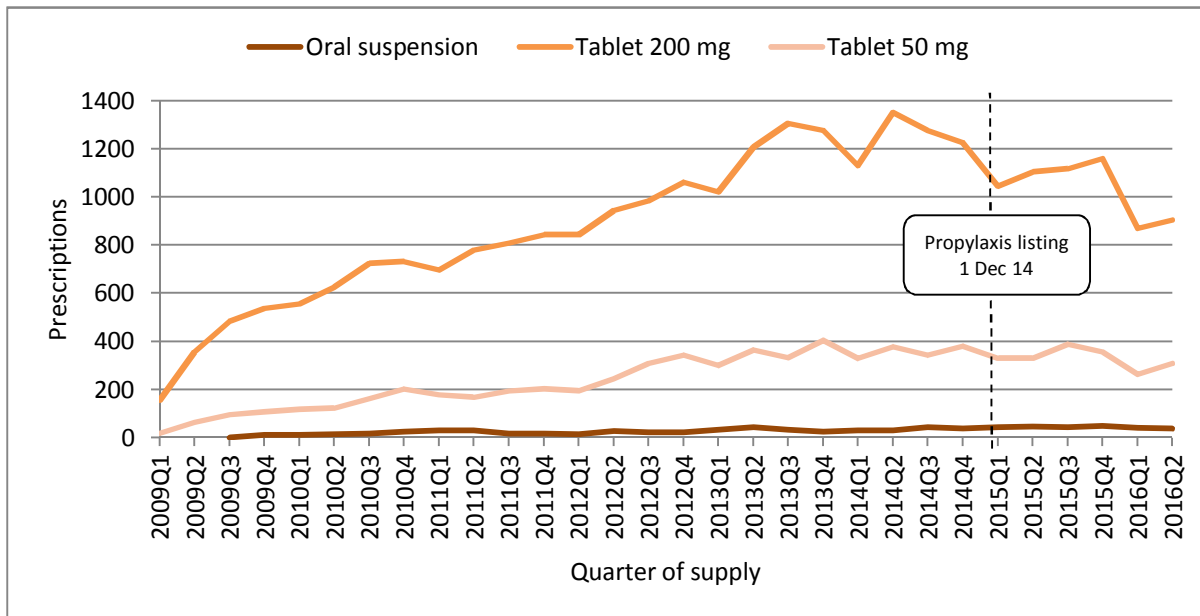


Figure 14: Voriconazole prescriptions by dosage form

Source: DUSC database, extracted August 2016.

The 200 mg voriconazole tablet remains the most utilised form of posaconazole. Utilisation of the 200 mg tablet appears to have peaked in early 2014 and decreased since. The utilisation of the 50 mg tablet and oral suspension appear to be stable since the end of 2012. The 50 mg tablet would typically be used in children who weigh less than 40 kg. Standard adult doses of voriconazole are 200 mg or higher. Refer to Dosing and Administration in Appendix 1 for further information.

Figure 15 presents voriconazole prescriptions supplied on the R/PBS by authority code.

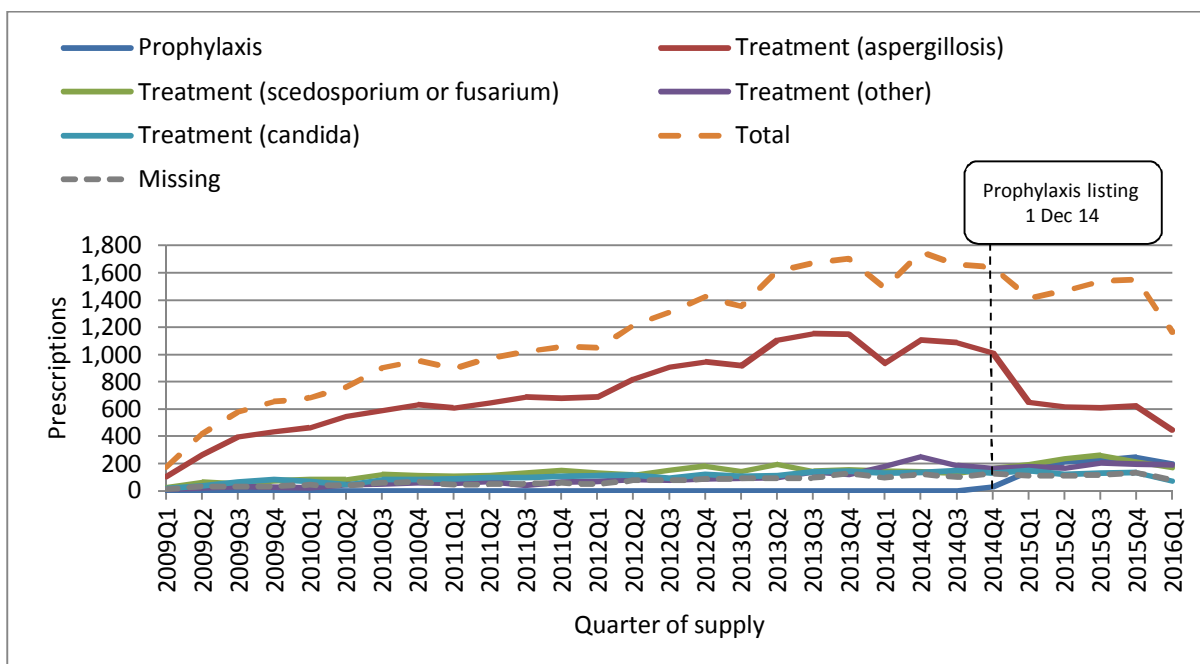


Figure 15: Voriconazole prescriptions by authority indication

Source: DUSC database, DHS Authority approvals database, extracted July 2016.

Note: There were 16 prescriptions with special DVA authority approvals that are not included in the figure due to small number per quarter.

The utilisation of voriconazole for the treatment of aspergillosis has almost halved since late 2014. Utilisation for all other treatment related indications increased during the same time period. Utilisation for prophylaxis has also added to voriconazole utilisation. However, the reduction in utilisation for aspergillosis has been larger than increased utilisation for treatment of other infections and utilisation for prophylaxis.

A substantial proportion of voriconazole prescriptions were not matched to an authority restriction code. In 2015, 8% of prescriptions could not be matched to an authority approval. In every single quarter, at least 5% of voriconazole prescriptions could not be matched to an authority approval.

Terbinafine

Figure 16 presents R/PBS prescriptions for terbinafine.

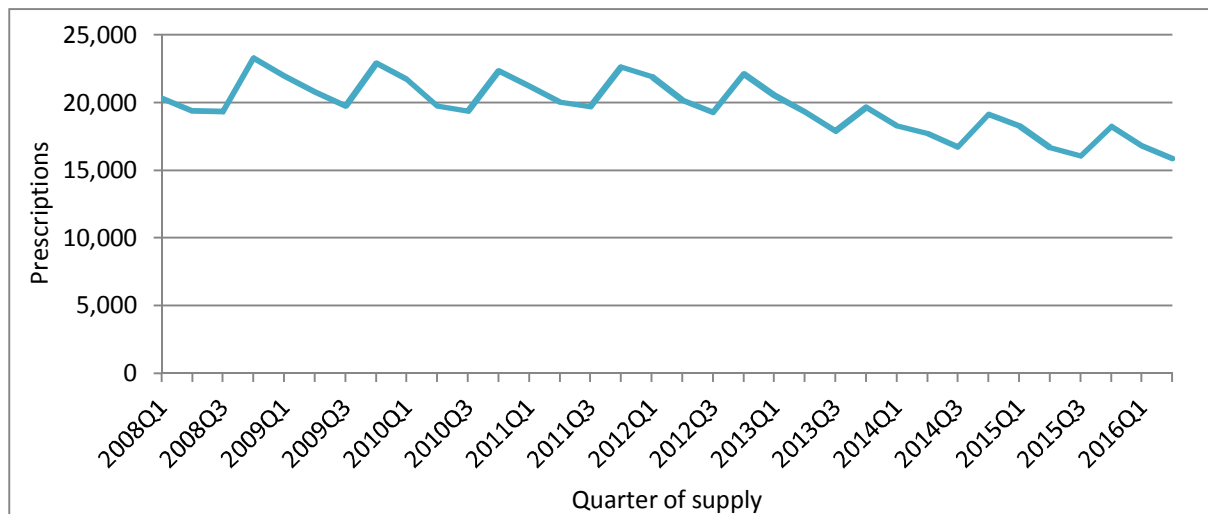


Figure 16: Terbinafine prescriptions

Source: DUSC database, extracted August 2016.

The number of terbinafine prescription supplied on the R/PBS was relatively stable from 2008 to 2013 and has since slowly declined.

Griseofulvin

Figure 17 presents griseofulvin prescriptions by strength.

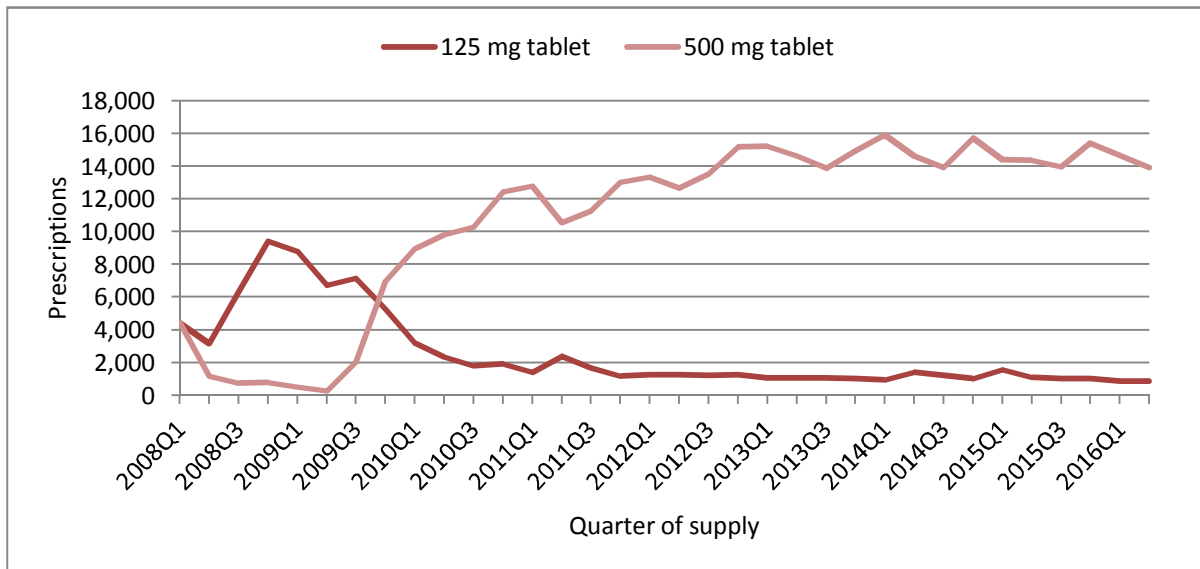


Figure 17: Griseofulvin prescriptions

Source: DUSC database, extracted August 2016.

Utilisation of griseofulvin has been relatively stable since 2013 with the 500 mg tablets continuing to be the most utilised strength.

Analysis of expenditure

Table 5 presents R/PBS expenditure on systemic antifungals by year.

Table 5: R/PBS expenditure on systemic antifungal medicines

	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16
Amphotericin B	\$13,628	\$5,376	\$59	-	-	-	-	-
Fluconazole	\$8,855,603	\$8,187,808	\$4,622,593	\$3,469,023	\$3,345,826	\$2,766,223	\$2,242,762	\$1,954,429
Griseofulvin	\$402,064	\$594,860	\$722,336	\$764,327	\$790,135	\$800,695	\$787,859	\$786,756
Itraconazole	\$1,730,637	\$1,744,580	\$1,868,454	\$2,061,139	\$2,367,412	\$2,588,335	\$2,829,234	\$2,810,165
Ketoconazole	\$581,608	\$555,233	\$557,888	\$605,749	\$627,407	\$243,273	-	-
Posaconazole	\$1,220,770	\$3,786,719	\$5,672,064	\$8,059,467	\$10,699,996	\$11,097,710	\$12,607,984	\$18,291,012
Terbinafine	\$7,361,147	\$7,036,579	\$6,742,756	\$6,001,831	\$3,656,012	\$2,247,584	\$1,583,211	\$1,050,616
Voriconazole	\$1,494,187	\$6,619,003	\$9,057,652	\$10,676,455	\$13,847,688	\$16,250,777	\$13,658,024	\$10,626,034
Total	\$21,659,645	\$28,530,159	\$29,243,801	\$31,637,991	\$35,334,476	\$35,994,598	\$33,709,074	\$35,519,012

Source: DHS Supplied Prescriptions Database, extracted August 2016

R/PBS expenditure on systemic antifungal medicines increased until the 2013-14 financial year. Expenditure decreased in 2014-15 but has increased in 2015-16. This is due to increasing expenditure on posaconazole which increased by over \$5.5 million in the 2015-16 financial year. The cost of fluconazole, terbinafine and voriconazole are decreasing.

Figure 18 presents R/PBS expenditure for systemic antifungals.

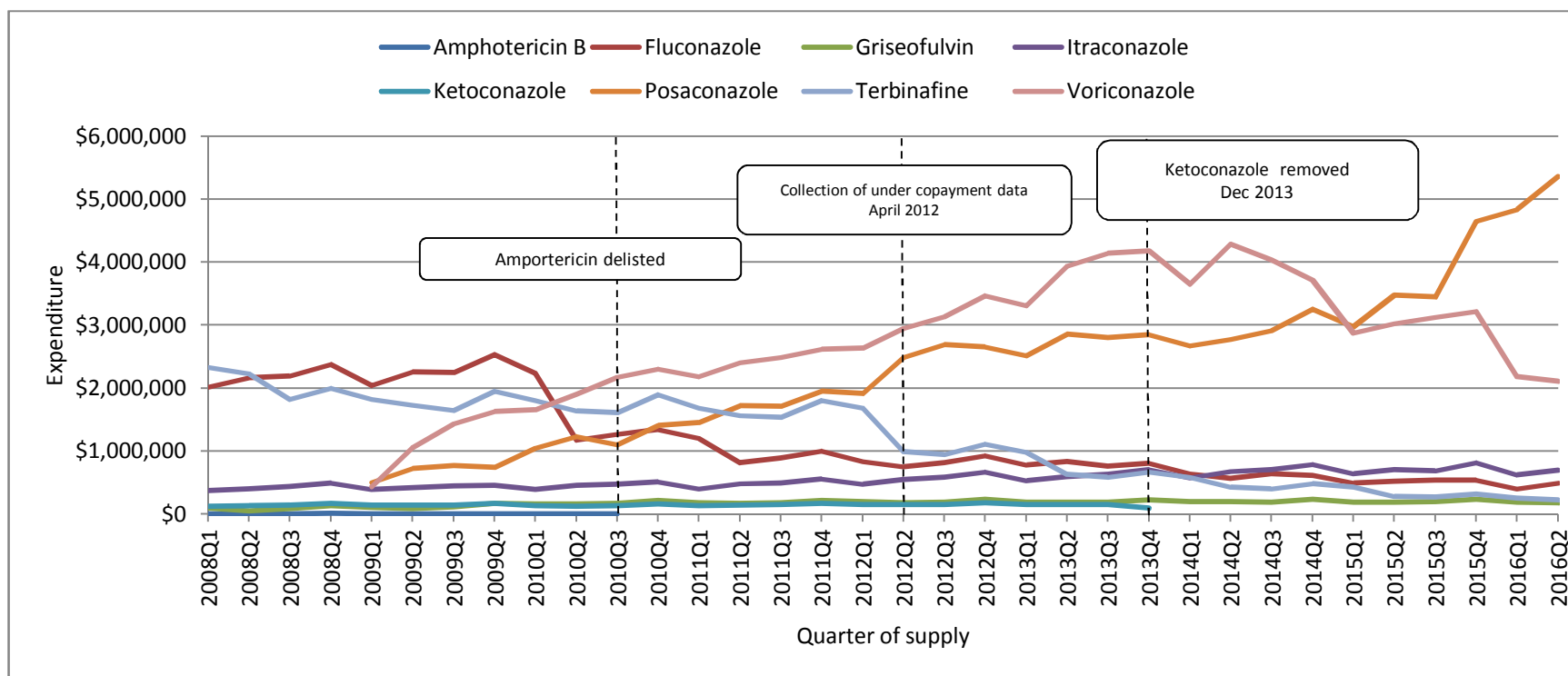


Figure 18: R/PBS expenditure on systemic antifungal medicines

Source: DUSC database, extracted August 2016.

Voriconazole expenditure has decreased due to decreased utilisation and price reductions. Generic brands of voriconazole tablets were PBS listed on 1 February 2016. Voriconazole had a price reduction on 1 February 2016. The DPMQ for 200 mg voriconazole tablets has decreased from \$2,631.18 in June 2013 to \$2,237.86 in June 2015. The current DPMQ is \$1,894.70.

As DUSC analyses are usually based on date of supply, this should be noted as there may be small differences between publicly available Medicare Australia date of processing data.

Analysis of actual versus predicted utilisation

Table 6 presents the predicted and actual utilisation of voriconazole for prophylaxis against invasive fungal infections. Utilisation was measured by two methods: one using the item codes for prophylaxis and the other using matched authority approval codes where the approval was for prophylaxis. There is a single authority code for all voriconazole prophylaxis indications, limiting the possibility of assessing utilisation by each high risk group.

Table 6: Predicted vs actual utilisation of voriconazole for prophylaxis

	Predicted	Actual	Percentage of predicted
Item Code			
Patients	-	357	-
Prescriptions	■	899	■
Expenditure	■	\$1,802,472	■
Authority Code			
Patients	-	336	-
Prescriptions	■	764	■
Expenditure	■	\$1,570,222	■

Source: DUSC database, DHS Authority approvals database, extracted August 2016

Utilisation of voriconazole for prophylaxis has been substantially lower than predicted. The utilisation of voriconazole for prophylaxis appears lower when authority codes are used to determine utilisation. This is because a proportion of supplied prescriptions could not be matched to an authority approval.

Figure 19 presents the utilisation of voriconazole items listed for prophylaxis.

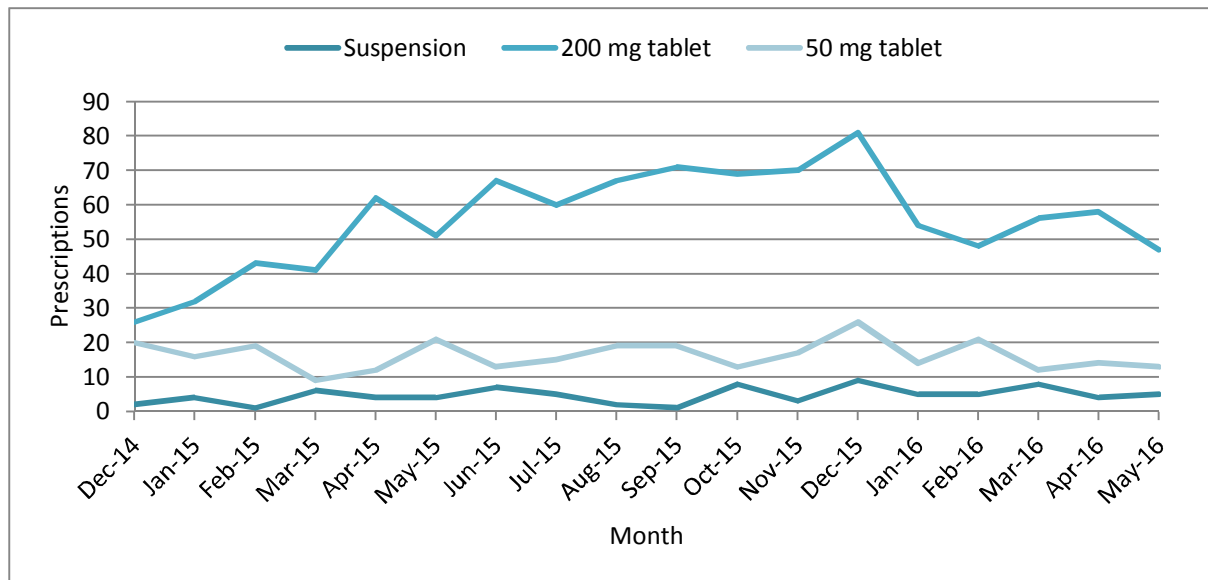


Figure 19: Voriconazole prescriptions for prophylaxis

Source: DHS Supplied Prescriptions Database, extracted July 2016

The number of voriconazole prescriptions for prophylaxis increased until December 2015 and decreased thereafter.

Discussion

Overall the utilisation of systemic antifungals listed on R/PBS decreased between the 2012/13 and 2014/15 financial years. This trend was seen in both prescription and patient data for this period (Table 3 and Table 4). In the 2015/16 financial year there was an increase in the number of patients treated, mainly driven by an increase in the number of patients treated with fluconazole. Of note is a substantial increase in the utilisation of fluconazole in the second quarter of 2016. This increase was mostly driven by increased utilisation of the 50 mg and 100 mg oral capsules. This increase occurred after the change in restriction level from streamlined authority to Restricted Benefit with no change to the indications in the restriction. This was mainly due to increased prescribing by GPs, followed by obstetricians and gynaecologists and dermatologists.

This may be due to prescribing for vulvovaginal candidiasis. This is supported by a large increase in the number of female patients supplied fluconazole capsules. Fluconazole 150 mg as a single dose is indicated for vaginal candidiasis where topical therapy has failed.³ There may be significant wastage and Quality Use of Medicines concerns if whole packs of fluconazole with 28 capsules are being prescribed for this indication. The US Centres for Disease Control state that repeated doses of fluconazole can be used to achieve remission in patients with recurrent vulvovaginal candidiasis.¹⁰ Dermatologists may be using fluconazole for dermatophyte infections.¹¹ Treatment of dermatophyte and vulvovaginal candidiasis may be outside the intended PBS listing for the treatment of serious or life-threatening candida infections. Until April 2010, the restriction wording for

fluconazole was for use in serious and life threatening candida infections was for patients unable to tolerate amphotericin B. The requirement for a patient to be unable to tolerate amphotericin B was removed from the restriction when amphotericin was discontinued and subsequently deleted from the PBS.

R/PBS utilisation of parenteral forms of fluconazole was decreasing until the second quarter of 2016. The number of 200 mg IV solution prescriptions supplied increased in the second quarter of 2016 after many quarters of declining utilisation. Surgeons and non-VR GPs had the largest increases in prescribing, suggesting there may be increased prescribing in the hospital setting. The availability of the oral suspension may have generally reduced the need to administer IV fluconazole to patients unable to take capsules. 90% of orally administered fluconazole is absorbed.³

The number of patients supplied posaconazole increased between the 2014-15 and 2015-16 financial years from 1,304 to 1,801. There has been an increase in the number of prescriptions supplied for treatment and prophylaxis indications. Since the introduction of the tablet formulation, utilisation of the oral suspension has declined substantially. R/PBS expenditure on posaconazole increased over \$5.5 million between the 2014-15 and 2015-16 financial years.

There is decreasing utilisation of voriconazole for the invasive aspergillosis indication. There is increasing utilisation of posaconazole for the same indication. The posaconazole listing for aspergillosis is for patients who are unable to tolerate or have disease that is refractory to alternative therapy. A future analysis of posaconazole utilisation could assess use of prior therapies on the PBS for patients starting posaconazole for treatment.

There are a number of other factors that may be contributing to decreasing voriconazole utilisation. In the prophylaxis setting, the voriconazole listing is limited to patients receiving an AlloHSCt sourced bone marrow of an unrelated donor or from umbilical cord blood. In 2013, 73% of AlloHSCts used peripheral blood stem cells and would not be eligible for PBS subsidy¹². Many AlloHSCt patients can probably access posaconazole under existing restrictions. Many patients receiving autologous or allogenic HSCTs for AML or MDS will meet criteria for posaconazole. These patients will typically receive chemotherapy and are likely to experience neutropenia as a part of the transplant protocol.¹³ In 2013, 267 haematopoietic stem cells transplants were performed on patients with AML or MDS, accounting for 15% of haematopoietic stem cells transplants.¹²

Posaconazole has a spectrum of activity that includes activity against zygomycetes¹⁴, a pathogen that can infect patients who have undergone HSCT.¹⁵ There may be a preference towards using a broader spectrum medicine. Acute GVHD occurs in 35-80% of AlloHSCt recipients, with a lower risk if the transplant was from a fully matched sibling¹⁶. Hospitals may supply posaconazole during this period to patients receiving a transplant for other conditions and use PBS supply if GVHD develops. Additionally, unlike the suspension, the posaconazole tablet formulation does not need to be taken with a fatty meal which may make it less difficult to take for patients undergoing intensive chemotherapy or GVHD.

There may be potential to expand listings for treatment to better match guidelines for treatment of fungal infections. No contemporaneous Australian evidence-based guidelines for the use of antifungals were identified. The current listings for fluconazole and itraconazole for the treatment of oesophageal candidiasis are only for immunosuppressed patients. The Infectious Diseases Society of America guidelines state that treatment is always required. Fluconazole is the recommended treatment. Itraconazole and voriconazole are recommended for fluconazole-refractory disease.¹⁷ Oesophageal candidiasis is rare in immunocompetent people. Infections in immunocompetent people has been associated with other potentially predisposing factors such as use of acid suppressing medicines, antibiotic use, systemic corticosteroid use and diabetes.¹⁸ Similarly, guidelines recommend itraconazole or voriconazole treatment for people with symptomatic chronic cavitary pulmonary aspergillosis.¹⁹

Actions undertaken by the DUSC Secretariat

A copy of the report was provided to sponsors of antifungal medicines and the Council of Australian Therapeutic Groups (CATAG) for comment.

DUSC consideration

Ketoconazole was delisted and deregistered in December 2013. DUSC commented that Table 3 shows prior to this 29,069 people were treated with ketoconazole in the July 2012 to June 2013 financial year. DUSC noted from Figure 1 of the report that it did not appear there was a corresponding increase in the use of other antifungals and questioned why patients previously taking ketoconazole would not use an alternative PBS listed antifungal.

DUSC noted that Figure 1 shows the use of fluconazole started to increase once its PBS listing changed from a streamlined authority listing to a Restricted Benefit listing in April 2016. DUSC further noted that single dose 150 mg oral fluconazole is available over the counter for the treatment of vaginal candidiasis but it may be cheaper for patients to be supplied fluconazole through the PBS. DUSC considered some over the counter use may have shifted to PBS prescriptions.

DUSC agreed that the data showed that use of fluconazole capsules by women has increased more than use by men (Figure 5). This indicates that the increased use of oral fluconazole may be due to prescribing for vulvovaginal candidiasis. The number of original prescriptions of fluconazole with no repeats has been increasing over time to exceed the number of prescriptions with five repeats (Figure 8). There has also been increased prescribing in some prescriber groups including general practitioners (GPs), gynaecologists and dermatologists. These trends also suggest fluconazole may be being prescribed for vulvovaginal candidiasis. DUSC was concerned that there may be significant wastage and quality use of medicines issues if whole packs of fluconazole with 28 capsules are being prescribed for this indication where only a single dose of one capsule is required.

Advice was sought from the Council of Australian Therapeutic Advisory Groups (CATAG) to investigate the rise in the use of PBS-listed IV fluconazole. To inform provision of this advice, CATAG requested that the data be provided by state, prescriber specialty and pharmacy type (public/private hospital). DUSC appreciated the advice of CATAG, which included a member survey involving all states and territories. CATAG advised that the increase in PBS use did not correlate with data from its jurisdictions. Public hospital based prescriptions for IV fluconazole were reported to have not increased or decreased. Data from 160 hospitals (20 private) captured in the National Antimicrobial Utilisation Surveillance Program showed there was a decrease in both oral and IV fluconazole in 2015-16. CATAG also reported that there were no changes in therapeutic guidelines. DUSC noted the further work undertaken by the DUSC Secretariat to determine if the increase in the use of fluconazole in quarter 2 of 2016 was localised. DUSC noted the analysis by state showed the number of prescriptions increased in all states, but the increase was highest in Queensland, Victoria and Western Australia (Attachment 1, Item 7.1). DUSC also noted Figure 7 showed that the biggest change in use of IV fluconazole by prescriber speciality was surgery, but this increase was only 64 prescriptions. DUSC commented that the increase in IV fluconazole in surgeons and non-vocationally registered GPs suggests there is an increase in prescribing in the hospital setting and DUSC questioned whether this was due to GPs working in hospitals. A further analysis undertaken by the Secretariat demonstrated that the number of 200mg vials of fluconazole supplied has increased in both private hospital pharmacies and community pharmacies (noting that some community pharmacies offer services to private hospitals). Overall prescription numbers were small but increases in supplies were most evident in community and private hospital pharmacies in Victoria, community pharmacies in Queensland and private hospitals in Western Australia.

The use of oral suspension posaconazole decreased with the introduction of the tablet formulation of posaconazole (Figure 11). DUSC noted the increase of use of the tablets appeared to have increased above the use of the oral suspension and that this is unsurprising given that the oral suspension is difficult to use.

DUSC noted the analysis of predicted versus actual utilisation showed the use of voriconazole for prophylaxis has been approximately 30% of predicted. DUSC considered this reflected a clinical preference for posaconazole over voriconazole which may relate to its wider spectrum of activity and new formulation which is better tolerated.

DUSC commented that the risk of resistance to antifungal medicines is not as large as resistance to antibiotics, but it has been documented. DUSC noted that there was a lack of contemporary Australian evidence-based guidelines for antifungal use.

DUSC requested that the use of fluconazole be monitored to see if the increased prescribing in the second quarter of 2016 continues. DUSC noted that several options may need to be considered if use continues to increase. Options could include seeking further input from infectious disease physicians on appropriate use, strengthening the clinical criteria to clarify treatment of severe or life threatening fungal infections rather than the simplified 'serious or life threatening', reintroducing the streamlined authority listing, providing education regarding use, or assessing whether oral fluconazole for vulvovaginal

candidiasis should be made available through the PBS with an appropriate quantity and no repeats.

DUSC actions

- DUSC considered that the use of fluconazole should continue to be monitored to examine whether the increase in use in the most recent quarter continues.
- DUSC requested that the report be provided to the PBAC.

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 following sponsors have no comment: Actavis Pty Ltd, Alphapharm Pty Ltd, Amneal Pharmaceuticals Pty Ltd, Apotex Pty Ltd, Arrow Pharma Pty Ltd, Aspen Pharma Pty Ltd, Dr Reddy's Laboratories Pty Ltd, Generic Health Pty Ltd, Janssen-Cilag Pty Ltd, Johnson & Johnson Pacific Pty Ltd, Mayne Pharma International Pty Ltd, Merck Sharpe & Dohme Pty Ltd, Novartis Pharmaceuticals, Pfizer Australia Pty Ltd, Ranbaxy Australia Pty Ltd, Sandoz Pty Ltd.

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: Dosage and administration

Table A1 presents the dosage of fluconazole recommended by the Product Information. Fluconazole can be used from birth using a less frequent dosing schedule.

Table A1: Dosage and administration of fluconazole

Indication	Dose and frequency of administration
Cryptococcal meningitis Serious and life-threatening candida infections	Adults: 400 mg on the first day. 200 mg daily for subsequent days. A dose 400 mg may be used. Children: 6-12 mg/kg daily as a single dose given daily. For candidal infections, patients should be treated for at least 4 weeks and for at least 2 weeks following symptom resolution. For cryptococcal meningitis, treatment should continue until should continue 10-12 weeks after cerebrospinal fluid becomes culture negative.
Prevention of cryptococcal meningitis relapse in AIDS patients	100-200 mg daily after full course of primary treatment.
Secondary prophylaxis against oropharyngeal candidiasis in patients with HIV infection.	150 mg as a single dose once weekly.
Vaginal candidiasis when topical therapy has failed	150 mg as a single dose.
Tinea infections	150 mg once weekly for 4 weeks.
Mucosal candidiasis (children)	3 mg/kg daily. A loading dose of 6 mg/kg may be used on the first day

Source: Fluconazole (Diflucan) Product Information

Table A2 presents itraconazole dosage and administration for adults based on the Sporanox brand of itraconazole. There are two brands of itraconazole listed on the PBS: Sporanox and Lozanoc. The doses are not equivalent. The recommended dose of Lozanoc is half the recommended dose for Sporanox. The table only includes indications that are relevant for the PBS listed conditions and populations.

Table A2: Dosage and administration of itraconazole (Sporanox brand)

Indication	Dose and frequency of administration Caution: Recommended doses only apply to Sporanox brand of itraconazole)
Aspergillosis	200 mg once daily for 2-5 months. 200 mg twice daily can be used for invasive or disseminated disease.
Histoplasmosis	200 mg once to twice daily for 8 months. Maintenance therapy 200 mg once daily.
Sporotrichosis	100 mg once daily for 3 months. Some patients may require 200 mg daily.
Systemic candidiasis	100-200 mg once daily. Treatment duration usually between 3 weeks and 7 months.

Indication	Dose and frequency of administration Caution: Recommended doses only apply to Sporanox brand of itraconazole)
Oral candidiasis (Immunosuppressed patients)	100-200mg daily for 4 weeks.

Source: Sporanox (itraconazole) Product Information.

Note: The PI states the safety and efficacy in children is not established. Itraconazole appears to be used in children in Australia.²⁰

Table A3 presents the dosage and administration information for posaconazole.

Table A3: Dosage and administration of posaconazole

Indication	Oral suspension	Tablets
Refractory invasive fungal infection	400 mg twice daily food. Daily dose can be given as 100 mg four times daily.	Loading dose of 300 mg twice daily on the first day. 300 mg once daily thereafter.
Oropharyngeal candidiasis (HIV infected patients)	200 mg once a day on the first day. 100 mg daily thereafter for 13 days.	No regimen specified in PI.
Prophylaxis of invasive fungal infections	200 mg three times daily.	Loading dose of 300 mg twice daily on the first day. 300 mg once daily thereafter.

Source: Posaconazole (Noxafil) Product Information.

Table A4 presents dosage and administration recommendations for voriconazole.

Table A4: Dosage and administration of voriconazole (tablets and suspension)

Indication	Dosage (>40kg)	Dosage (<40kg)
Loading dose (all indications)	400 mg every 12 hours for the first 24 hours	200 mg every 12 hours for the first 24 hours
Serious Candida infections Invasive aspergillosis; Scedosporium and Fusarium infections; other serious mould infections	200 mg twice daily	100 mg twice daily
Prophylaxis of invasive fungal infections	200 mg every 12 hours	100 mg every 12 hours

Source: Voriconazole (Vfend) Product Information.

The maintenance dose may be increased to 300 mg twice daily or 150 mg twice daily for patients who weigh less than 40 kg if the response is inadequate.

Terbinafine is given at a dose of 250 mg once daily. The duration of treatment ranges from two weeks to three months depending on the site of infection.

Griseofulvin is given at a standard dose of 500 mg per day for adults. Doses of up to 1,000 mg may be required for some infections, such as nail infections, until response is seen. In children, a dose of 10 mg/kg in divided doses. The duration of treatment depends on the site of infection. Treatment should be continued for at least two weeks after all signs of the infection have disappeared.