

Posaconazole tablets: Predicted vs actual analysis

Drug utilisation sub-committee (DUSC)

May 2018

Abstract

Purpose

To compare the predicted and actual use of posaconazole for the treatment and prophylaxis of fungal infections since the tablet form listed on the Pharmaceutical Benefits Scheme (PBS) in September 2015.

PBS Listing (abridged)

Posaconazole is listed on the PBS for the:

- treatment of invasive aspergillosis and other specified fungal infections in patients who are unable to tolerate, or have disease refractory to, alternative therapy.
- prophylaxis of invasive fungal infections in specific high risk groups:
 - patients with anticipated neutropenia whilst receiving chemotherapy for acute myeloid leukaemia or myelodysplastic syndrome
 - patients with acute (grade II-IV), or extensive chronic, graft versus host disease and who are receiving intensive immunosuppressive therapy following an allogenic haematopoietic stem cell transplant.

Data Source

Data to assess the utilisation of posaconazole and other azole antifungals listed on the PBS was obtained from the Department of Human Services (DHS) PBS prescription claims database.

Key Findings

- In 2017, compared with 2014 (the calendar year prior to listing of the tablet formulation) the number of PBS prescriptions of posaconazole more than doubled.
- Changes in the utilisation of posaconazole are mainly driven by the prophylaxis indication as this comprises approximately two thirds of prescriptions dispensed. However, towards the end of 2017 there was an upswing in the utilisation of posaconazole for the treatment of 'other' fungal infections. As a result, in December 2017 only 53% of prescriptions were for prophylaxis.

- The number of incident patients commencing posaconazole has increased. In the two years prior to the listing of the tablet form, an average of 73 patients commenced posaconazole each month. In the two years after the tablet listed this increased to 110 patients per month.
- The increasing utilisation of posaconazole seems to be due to a combination of more patients initiating treatment and slightly longer durations of treatment with the tablets compared with the oral liquid. The cohort of patients initiating on posaconazole for prophylaxis in 2014 had a median time (excluding breaks) on treatment of 86 days. For a cohort initiating from September 2015 to August 2016 (inclusive) the median time on treatment was 96 days.
- A time to refill analysis shows similar time to dispensing of the tablet and the liquid form indicating that adherence may be similar for the two formulations.
- The use of voriconazole for prophylaxis of fungal infections is low and remained relatively unchanged following the listing of posaconazole tablets. The increase in posaconazole use cannot be attributed to substitution from voriconazole.

Purpose of analysis

To compare the predicted and actual use of posaconazole for the treatment and prophylaxis of fungal infections since the tablet form listed on the Pharmaceutical Benefits Scheme (PBS) in September 2015.

When recommending posaconazole tablets for listing on the PBS, the Pharmaceutical Benefits Advisory Committee (PBAC) considered that utilisation of posaconazole tablets should be reviewed by DUSC after listing, noting that usage was likely to increase due to ease of use of tablets over liquid. The Committee considered it uncertain whether any additional patient benefit from such increased use would accrue.¹

Background

Posaconazole is a broad-spectrum azole antifungal with activity against some yeasts and moulds not generally responsive to azoles, or resistant to other azoles, including species of *Candida*, *Aspergillus*, and organisms not previously regarded as being susceptible to azoles, such as the zygomycetes.²

The other azole antifungals for systemic fungal infections are fluconazole, itraconazole and voriconazole. Fluconazole is active against yeasts, including *Candida* species and *Cryptococcus*. Itraconazole has activity against yeasts and *Aspergillus* species. Voriconazole is active against yeasts, *Aspergillus* species, and some *Scedosporium* and *Fusarium* species.³

Therapeutic Goods Administration (TGA) approved indications²

Posaconazole is indicated for use in the treatment of the following invasive fungal infections in patients 13 years of age or older:

- 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.

Posaconazole is also indicated for the:

- 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.

¹ <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2015-03/posaconazole-noxafil-psd-03-2015>

² NOXAFIL® (Posaconazole). Australian Approved Product Information. Sydney: Merck Sharp & Dohme (Australia) Pty Limited. Approved 15 March 2006, updated 29 September 2017. Available from <https://www.tga.gov.au/product-information-pi>

³ Antifungal drug information. Published November 2014. Amended June 2015. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; March 2018 edition.

- 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.

The PBS restrictions are narrower than the TGA approved indications in that PBS subsidy for prophylaxis is limited to the high risk groups where proven benefit was shown in clinical trials, and treatment of oropharyngeal candidiasis in immunocompromised adults is not PBS listed. See the ‘PBS listing details’ and ‘Relevant Aspects of PBAC Consideration’ sections for further details.

Dosage and administration²

Posaconazole oral suspension⁴ should be administered with a full meal or with a liquid nutritional supplement in patients who cannot eat a full meal. Posaconazole modified release tablets need to be swallowed whole but may be taken without regard to food intake. The modified release tablet and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation.

Table 1: Dosage and administration of posaconazole

Indication	Oral suspension	Tablets
Refractory invasive fungal infection (IFI) / intolerant patients with IFI	400 mg (10 mL) twice daily with a meal or 240 mL of nutritional supplement.	Loading dose of 300 mg (three 100 mg modified release tablets) twice a day on the first day, then 300 mg (three 100 mg modified release tablets) once a day thereafter. Duration of therapy should be based on the severity of the patient’s underlying disease, recovery from immunosuppression, and clinical response.
Oropharyngeal candidiasis (HIV-infected patients)	Loading dose of 200 mg (5 mL) once a day on the first day, then 100 mg (2.5 mL) once a day for 13 days.	None specified.
Prophylaxis of invasive fungal infections	200 mg (5 mL) three times daily with a meal or with a nutritional supplement in patients who cannot tolerate food. Duration of therapy is based on recovery from neutropenia or immunosuppression.	Loading dose of 300 mg (three 100 mg modified release tablets) twice a day on the first day, then 300 mg (three 100 mg modified release tablets) once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression.

⁴ Note that according to the Product Information posaconazole is a suspension formulation. The PBS schedule describes it as an oral liquid. Both terms are used in this report.

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

PBS listing details

Posaconazole 40 mg/mL oral liquid and 100mg modified release tablets were listed on the PBS on 1 January 2009 and 1 September 2015, respectively.

Table 2 presents the PBS listing of posaconazole (current as at 1 April 2018).

Table 2: PBS listing of posaconazole

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
9360P	Posaconazole 40 mg/mL oral liquid, 105 mL	1	..	\$691.97	Noxafil [MK]
10460M	Posaconazole 100 mg modified release tablet, 24	1	..	\$834.65	Noxafil [MK]

Source: the PBS website.

PBS Restriction

Authority required (telephone) for the treatment of the following fungal infections in patients who are unable to tolerate alternative therapy or have disease refractory to alternative therapy:

- Invasive aspergillosis
- Fusariosis
- Zygomycosis
- Coccidioidomycosis
- Chromoblastomycosis
- Mycetoma

Authority required (telephone) for the prophylaxis of invasive fungal infections including both yeasts and moulds in patients who are:

- considered at high risk of developing an invasive fungal infection due to anticipated neutropenia (an absolute neutrophil count less than 500 cells per cubic millimetre), for at least 10 days whilst receiving chemotherapy for acute myeloid leukaemia or myelodysplastic syndrome; OR
- considered at high risk of developing an invasive fungal infection due to having 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

For prophylaxis, no more than 6 months' therapy per episode will be PBS subsidised.

The restriction for tablets (but not the liquid) states that treatment of neutropenia should continue until recovery of the neutrophil count to at least 500 cells per cubic millimetre,

and that patients who have had a previous invasive fungal infection should have secondary prophylaxis during subsequent episodes of neutropenia.

A note to the restriction allows applications for an increased maximum quantity for up to 1 month supply and repeats sufficient for up to 6 months' supply to be authorised. Based on the recommended doses in Table 1, one pack of tablets provides a sufficient quantity for approximately 7 days of treatment or prophylaxis. One bottle of oral liquid provides a quantity sufficient for approximately 5 days of treatment or 7 days of prophylaxis.

For full details of the current PBS listing refer to the PBS website.

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

Posaconazole

The PBAC recommended the listing of posaconazole oral suspension at the July 2006 meeting for the treatment of invasive aspergillosis and other fungal infections (fusariosis, zygomycosis, coccidioidomycosis, chromblastomycosis, mycetoma) in patients intolerant to, or with disease refractory to, other therapy.

The recommendation was made on the grounds of high but acceptable cost-effectiveness compared to a suite of salvage therapies. The submission had nominated voriconazole as the major comparator. The PBAC considered other salvage therapies including caspofungin, and amphotericin B lipid complex were also appropriate comparators because voriconazole is unlikely to be the only drug chosen for treatment of all the conditions in the listed indication.

At the time of recommendation, the current standard first line therapy for proven or probable acute invasive aspergillosis according to the Australasian Society for Infectious Diseases (ASID): Guidelines for use of antifungal agents in treatment of invasive fungal infection (July 2003), was conventional amphotericin B, voriconazole, liposomal amphotericin B, amphotericin B lipid complex or caspofungin. Among these anti-fungal agents recommended by ASID, only conventional amphotericin was PBS listed for first line therapy. Conventional amphotericin B (deoxycholate) was subsequently discontinued and deleted from the PBS in mid-2010.

The July 2006 recommendation was not implemented due to financial considerations. In March 2008 the PBAC considered a resubmission which provided revised economic and financial estimates. The listing was implemented January 2009.

For further details refer to the Public Summary Document from the July 2006 PBAC meeting.

The PBAC recommended the listing of posaconazole oral suspension at the March 2008 meeting for the prophylaxis of invasive fungal infections, including both yeasts and moulds, in a patient who is at high risk of developing these infections and who meets certain criteria, based on acceptable cost-effectiveness compared with fluconazole and

itraconazole.

The PBAC considered that posaconazole was superior to fluconazole and itraconazole in the trial populations. However, the PBAC noted that the population in the trials did not reflect all populations for whom PBS listing was sought, such as solid organ transplants for liver, lung and pancreas. The PBAC considered that the listing should be restricted to the populations in trial 1899 and trial 316, where proven benefit was shown in patients with prolonged neutropenia and in patients with severe GVHD who are at high risk of invasive fungal infection. The PBAC considered that PBS-subsidised treatment with posaconazole in the GVHD population should be limited to 6 months based on the median duration of treatment in trial 316 of 111 days (range 1-138).

The PBAC recommended removal of the age restriction to enable access for paediatric patients noting that posaconazole is not contraindicated in children.

For further details refer to the Public Summary Document from the March 2008 PBAC meeting.

At the March 2015 meeting, the PBAC recommended the listing of posaconazole tablets for the same prophylaxis and treatment of invasive fungal infections criteria as the oral suspension. The PBAC considered that the tablets provide the same benefits as seen with posaconazole liquid but with the potential for greater ease of administration; as the tablet formulation does not need to be taken with food.

The PBAC noted the TGA recommendation that the tablet and liquid forms of posaconazole are not considered interchangeable due to the differing treatment regimens and considered that the two formulations should not be able to be substituted on the PBS.

The PBAC noted that due to the differing treatment regimens between the tablet and liquid preparations, it was not possible to calculate equi-effective doses or a simple comparative price per milligram. The PBAC considered that the price per treatment course should be equivalent for the two formulations of posaconazole.

The PBAC considered that duration of therapy is a significant source of uncertainty. As there are no conclusive data to inform a clinical decision to discontinue treatment or discontinue prophylaxis in chronic GVHD, the PBAC considered that there is a risk that patients will persist on treatment in the absence of clear additional clinical benefit.

The submission had proposed that the listing of posaconazole would be cost neutral. The PBAC considered that utilisation of posaconazole tablets should be reviewed by DUSC after listing, noting that usage was likely to increase due to ease of use of tablets over liquid. The Committee considered that it was 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.

The PBAC considered that there may be uptake from the current voriconazole market, and that the market share of posaconazole may increase with listing of the tablet formulation.

For further details refer to the Public Summary Document from the March 2015 PBAC meeting.

Other relevant considerations

Voriconazole was recommended for PBS listing for treatment indications at the June 2003 PBAC meeting.

At the March 2014 meeting, the PBAC recommended an extension to the listing of voriconazole to include an Authority Required listing for prophylaxis against invasive fungal infections in the high risk patients groups of acute myeloid leukaemia (AML); high-risk myelodysplastic syndrome (MDS); GVHD; and high risk allogeneic haematopoietic stem cell transplant (AlloHSCT) recipients.

The PBAC's recommendation was 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 considered the submission's proposed clinical place for voriconazole as an alternative antimicrobial for prophylaxis against invasive fungal infections, including both yeasts and moulds, to be reasonable.

The PBAC accepted posaconazole as the appropriate comparator. Fluconazole and itraconazole were also accepted by the PBAC as secondary comparators.

For further details refer to the Public Summary Document from the March 2014 PBAC meeting

Clinical Guidelines

Prophylaxis

The Consensus Guidelines for Antifungal Prophylaxis in Haematological Malignancy and Haematopoietic Stem Cell Transplantation⁵ consider that risk stratification is key to identifying patients that should be considered for antifungal prophylaxis. The guidelines also note that risk stratification can be complex. The consensus guidelines identify two groups of patients as having the highest risk of developing invasive fungal disease and these align with the PBS subsidised population for posaconazole (patients receiving intensive chemotherapy for AML or MDS, and certain patients with GVHD following AlloHSCT). The

⁵ Fleming et al. Consensus guidelines for antifungal prophylaxis in haematological malignancy and haematopoietic stem cell transplantation. Internal Medicine Journal 44 (2014).

Consensus Guidelines⁵ and the Therapeutic Guidelines⁶ also consider that prophylaxis is sometimes indicated for solid organ transplant (liver and heart and/or lung) and autologous haematopoietic stem cell transplant (HSCT) recipients. Other high risk patient groups, sometimes indicated, are patients with acute lymphocytic leukaemia (ALL); some forms of non-Hodgkin lymphoma and multiple myeloma patients depending on the chemotherapy regimen and its duration.^{5,6}

The Consensus Guidelines for Antifungal Prophylaxis in Haematological Malignancy and Haemopoietic Stem Cell Transplantation note posaconazole is the preferred agent for use in high risk patient groups given its broad anti-fungal activity. Voriconazole is an alternative to posaconazole because it exhibits mould activity. Itraconazole may also be an alternative (but is not specifically listed on the PBS for the prophylaxis of fungal infections).

For AlloHSCT patients with GVHD the Therapeutic Guidelines recommend that prophylaxis for invasive fungal disease continues until day 100 or until prednisolone dose is less than 15mg, whichever is later.⁶ The Consensus Guidelines recommend that prophylaxis should continue for 16 weeks or until corticosteroid dose is less than 10 mg daily prednisolone equivalent.⁵ The PBS restriction limits treatment to 6 months per episode.

For leukaemia the Therapeutic Guidelines and Consensus Guidelines recommend starting prophylaxis on day 1 of chemotherapy and continuing until the neutrophil count recovers (more than $0.5 \times 10^9/L$). This is consistent with the PBS restriction.

Treatment

For treatment of invasive fungal infections, the duration of treatment depends on the patient's clinical and mycological response, and resolution of immunosuppression.^{6,7} The optimal length of treatment of invasive aspergillosis is uncertain but 6-12 weeks is common. For fusariosis least 12 weeks of treatment is often required.

Approach taken to estimate utilisation

The minor submission used a market-share approach based on packs (units) dispensed to estimate the extent of use of the tablet form of posaconazole. The submission assumed that the listing would be cost neutral to the PBS given that the tablets were expected to be used in patients that would otherwise have been treated with the oral suspension. A conversion factor was applied because when used for refractory treatment one bottle of oral liquid provides a slightly shorter duration than one pack of tablets.

⁶ Prevention of infection: immunosuppressed patients [published November 2014]. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; March 2018 edition.

⁷ Blyth et al. Consensus guidelines for the treatment of invasive mould infections in haematological malignancy and haemopoietic stem cell transplantation, 2014. Internal Medicine Journal 44 (2014)

Key assumptions included:

- that 66% of posaconazole use is for prophylaxis and 34% is for refractory treatment.
- there would be linear growth in the posaconazole market (based on extrapolation of utilisation data from 2009-2014).
- uptake of the tablet of █% in Year 1 (assuming a 1 August PBS listing date), █% in year, 2 then increasing to █% by year 5. The forecast uptake of the tablets was based on voriconazole use as this antifungal has both a tablet and suspension form available on the PBS. Additionally it was assumed prescribers would shift quickly to the tablet form of posaconazole.
- the liquid would continue to be used in a small number of patients unable to swallow a tablet.

Previous reviews by the DUSC

DUSC examined the utilisation of antifungals for systemic use at its meeting in October 2013. Utilisation of antifungal medicines had increased during the period of January 2008 to December 2012. DUSC considered that this increasing use reflected a larger number of immunocompromised patients in the community.

Antifungal medicines for systemic use were again reviewed by DUSC at its meeting in September 2016. The analysis included fluconazole, itraconazole, posaconazole, voriconazole, terbinafine and griseofulvin. The review found that terbinafine and griseofulvin were the most widely used medicines and that the number of fluconazole, itraconazole and posaconazole prescriptions had increased over time. The use of voriconazole for prophylaxis was very low.

Script volume for posaconazole was low in the systemic antifungal medicine market, particularly when compared with medicines such as fluconazole yet posaconazole accounted for the largest proportion of government expenditure within this market.

For details of the DUSC consideration of, antifungals for systemic use refer to the Public Release Document from the September 2016 DUSC meeting.

Methods

This analysis uses data from the Department of Human Services (DHS) supplied prescriptions database and the DHS Authority Approvals database. The DHS supplied prescriptions database includes data submitted to DHS for payment of a PBS or Repatriation PBS (RPBS) subsidy by the Government by all approved pharmacies in Australia. The DHS Authority Approvals database contains additional information in support of a PBS authority required prescriptions such as a restriction code and can be matched to the supplied prescriptions database.

Prescriptions for posaconazole and other antifungals (all medicines in the ATC groups J02A and D01BA) supplied from January 2013 to the end of December 2017 were extracted.

An incident (or 'new' patient) was determined based on the date of first supply of PBS subsidised posaconazole. A prevalent patient is a patient with at least one prescription supplied in the specified time period.

To count prescriptions by authority indication, data from the DHS supplied prescriptions database was merged with data from the DHS Authority approvals database. This allowed the derivation of the clinical indication for each script supplied. Scripts without an indication code are reported separately (unknown). Authority codes for posaconazole and voriconazole were categorised into three indications, treatment for aspergillosis, treatment for other fungal infections, and prophylaxis.

Time to refill analysis

Time to refill analysis was PBS item and indication specific. That is, a prescription for a particular PBS item (ie. form and strength) and indication was only deemed to be refilled by a prescription of the same form and strength to the same patient (ie. not by another form and strength of the medicine).

Length of treatment analysis

The length of treatment analysis used the Kaplan Meier method (aka Product-Limit method). The length of treatment measure that was used excluded any breaks in treatment. A break in treatment was defined as a gap of more than 3 times the median time to resupply, which was an estimated break in treatment of at least 2 times the median time to resupply. A patient was deemed to be continuing treatment (classified as censored in the Product-Limit method) at the end of the data period (i.e. the end of December 2017) if their last prescription was within 3 times the median time to resupply of this end date. The continuing patient's length of treatment was based on the treatment coverage end date which was the end of the data period or the supply date of their last prescription plus the median time to resupply, whichever was later.

As the analyses in the report use date of supply prescription data, there may be small differences compared with publicly available Department of Human Services (DHS) Medicare date of processing data.⁸

⁸ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

Results

Overall utilisation

Figure 1 presents the number of prescriptions of posaconazole. Voriconazole is also included for context as it has similar PBS restrictions (see Appendix A) and the PBAC considered that there may be some uptake of posaconazole tablets from the voriconazole market.

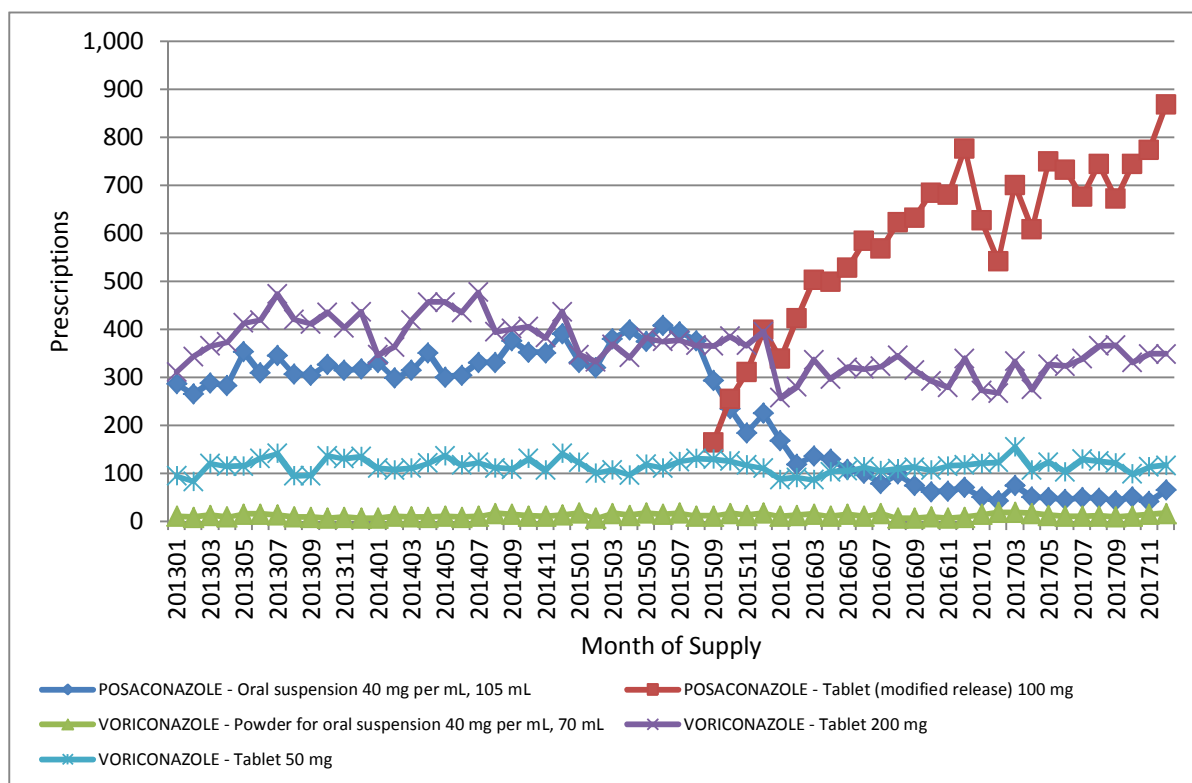


Figure 1: Prescriptions by form of posaconazole and voriconazole

Source: DHS supplied prescriptions database; extracted 09 March 2018.

Uptake of the tablet formulation of posaconazole was rapid and there was a sharp decline in prescriptions for the oral liquid. The availability of the tablet formulation resulted in substantial growth in the overall use of posaconazole.

Utilisation of voriconazole 50mg tablet and oral suspension has remained low and stable. The use of voriconazole 200mg tablets was in decline prior to the listing of posaconazole tablets, but decreased further in late 2015.

The utilisation of posaconazole and voriconazole is low in the context of the overall azole antifungal market (see Appendix B).

Figure 2 presents the number of posaconazole prescriptions by indication. The use of posaconazole for both treatment and prophylaxis was stable until mid-2015. There was a noticeable increase in use for both treatment and prophylaxis following the listing of the tablet form from 1 September 2015, with the largest increase evident for prophylaxis. Use for the treatment of aspergillosis and for prophylaxis has since stabilised. In the second half of 2017 there was a sharp increase in use of posaconazole for the treatment of ‘other’ fungal infections (fusariosis, zygomycosis, coccidioidomycosis, chromoblastomycosis, mycetoma). The reason/s for this increased use is unknown.

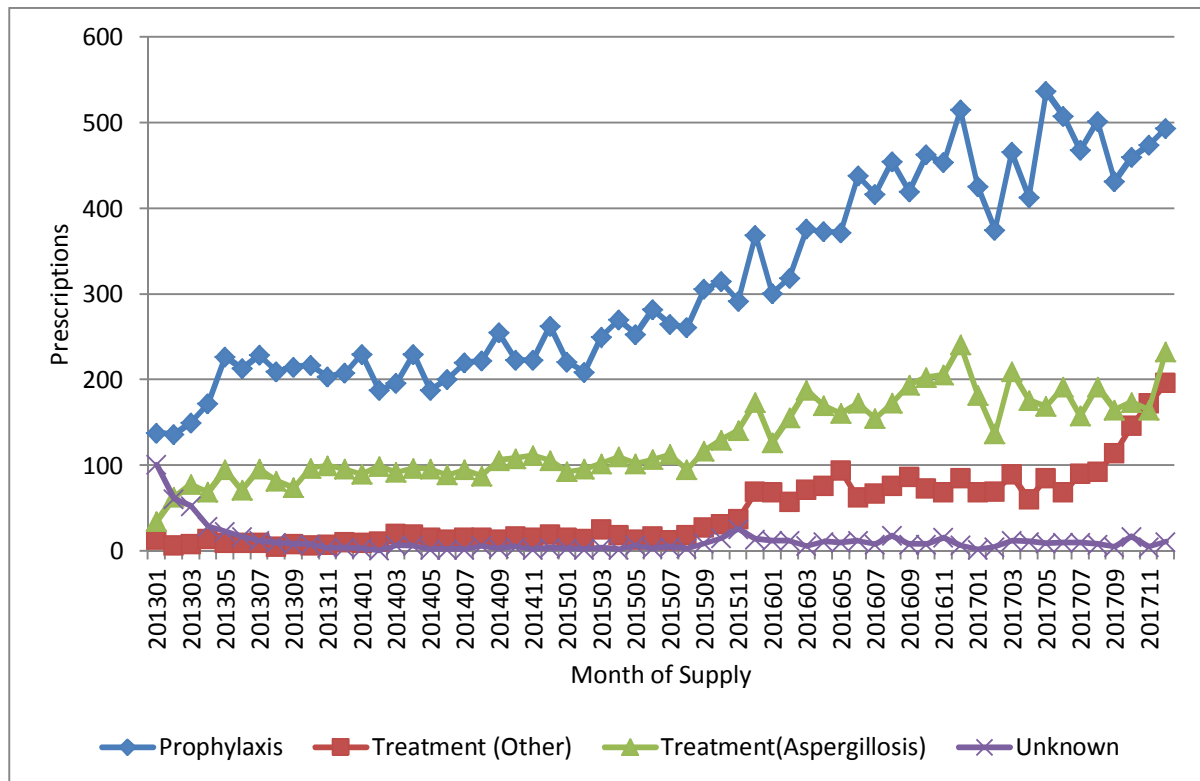


Figure 2: Posaconazole prescriptions by indication

Indications were determined by authority codes from the Authority Approvals Database (AAD).

Source: DHS AAD, DHS supplied prescriptions database to 31 December 2017; extracted 13 March 2018.

The majority of prescriptions of posaconazole are for prophylaxis. In the 12 month periods before and after the listing of the posaconazole tablets, approximately two thirds of prescriptions were for prophylaxis and one third for treatment indications. The proportion of use for treatment has increased in the most recent year because of the upswing in use for ‘other’ fungal infections.’ In December 2017 only 53% of prescriptions were for prophylaxis.

The large change in utilisation following availability of the tablet form, apparent in Figures 1 and 2, cannot be accounted for by the quantity per prescription differing between the forms. A prescription of posaconazole can be authorised for up to one month’s supply and with repeats sufficient for up to 6 months’ supply. Based on the recommended doses in Table 1, one pack of tablets provides a sufficient quantity for 7-8 days of treatment or prophylaxis. One bottle of oral liquid provides a quantity sufficient for approximately 5-6

days of treatment or 7-8 days of prophylaxis. The median number of packs per prescription dispensed for both the tablet and the suspension was 4 (data not shown).

Figure 3 presents the number of voriconazole prescriptions by indication. Voriconazole is mainly used for the treatment of fungal infections, and unlike posaconazole is not limited to use in disease refractory to, or in patients intolerant to, alternative therapy. During the first half of 2015 there was a decline in the use of voriconazole for treatment of aspergillosis, with a further small decline following the listing of posaconazole tablets.

A low proportion of the use of voriconazole is for prophylaxis. Voriconazole was PBS listed for prophylaxis in certain high risk groups from 1 December 2014 and had established a small market share that was largely unchanged by the listing of posaconazole tablets.

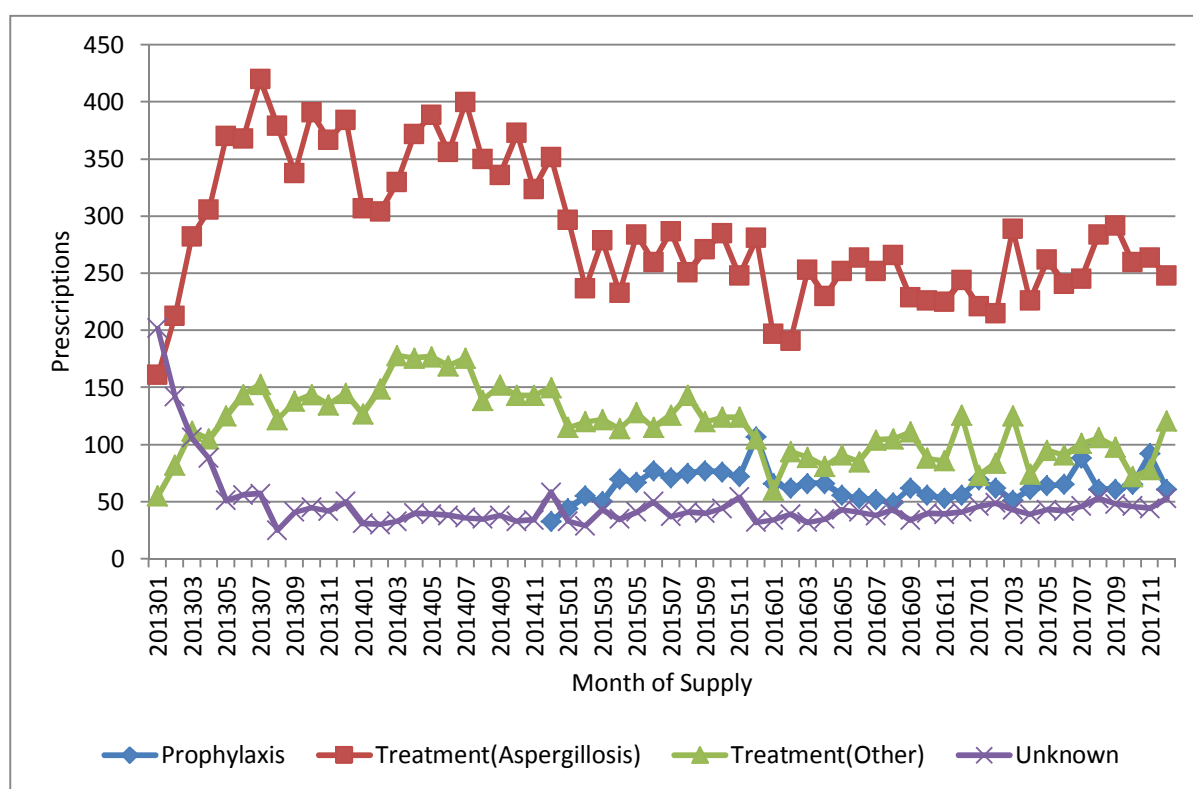


Figure 3: Voriconazole prescriptions by indication

Indications were determined by authority codes from the Authority Approvals Database (AAD).

Source: DHS AAD, DHS supplied prescriptions database to 31 December 2017; extracted 13 March 2018.

Figure 4 presents the total number of new and prevalent patients on either form of posaconazole. Figure 5 provides the number of prevalent and incident posaconazole patients stratified by form & strength, and Figure 6 presents prevalent and incident patients for prophylaxis only. An incident patient is defined as a first PBS supply of posaconazole.

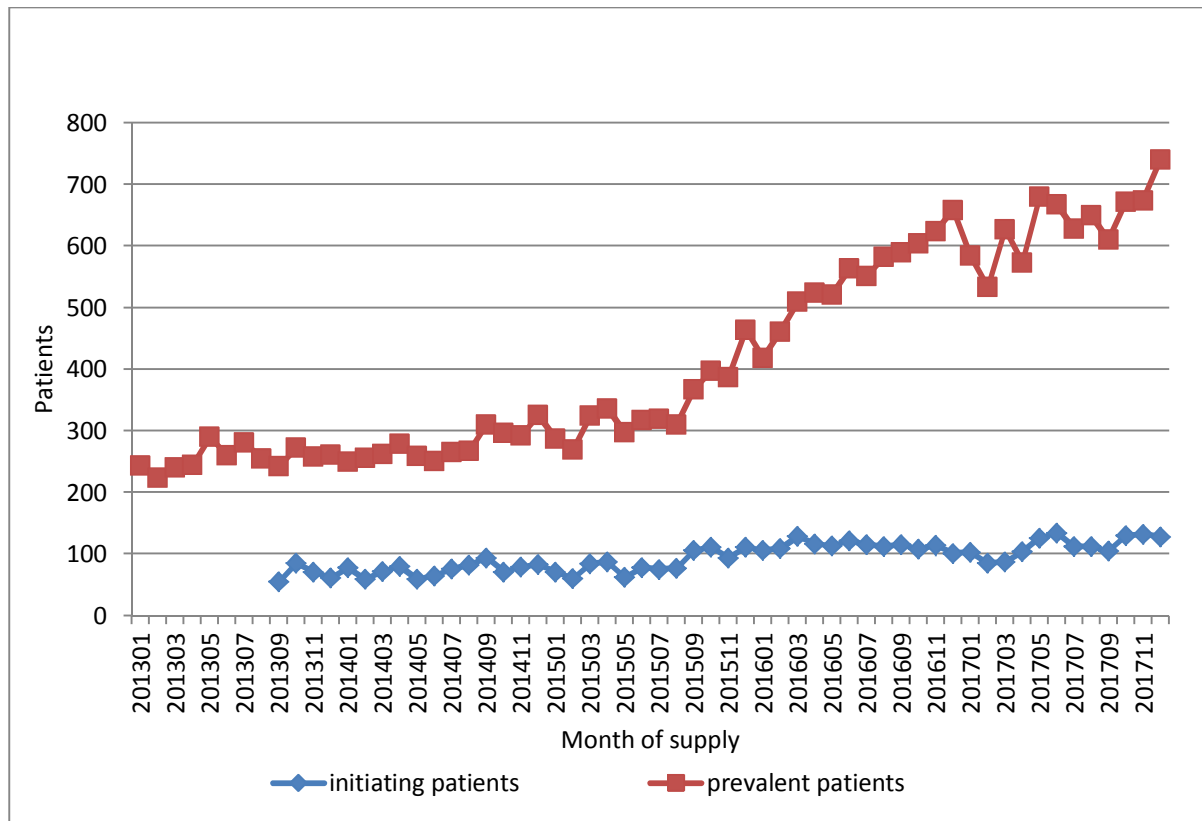


Figure 4: Incident and prevalent patients on either form of posaconazole

Source: DHS AAD, DHS supplied prescriptions database to 31 December 2017; extracted 13 March 2018.

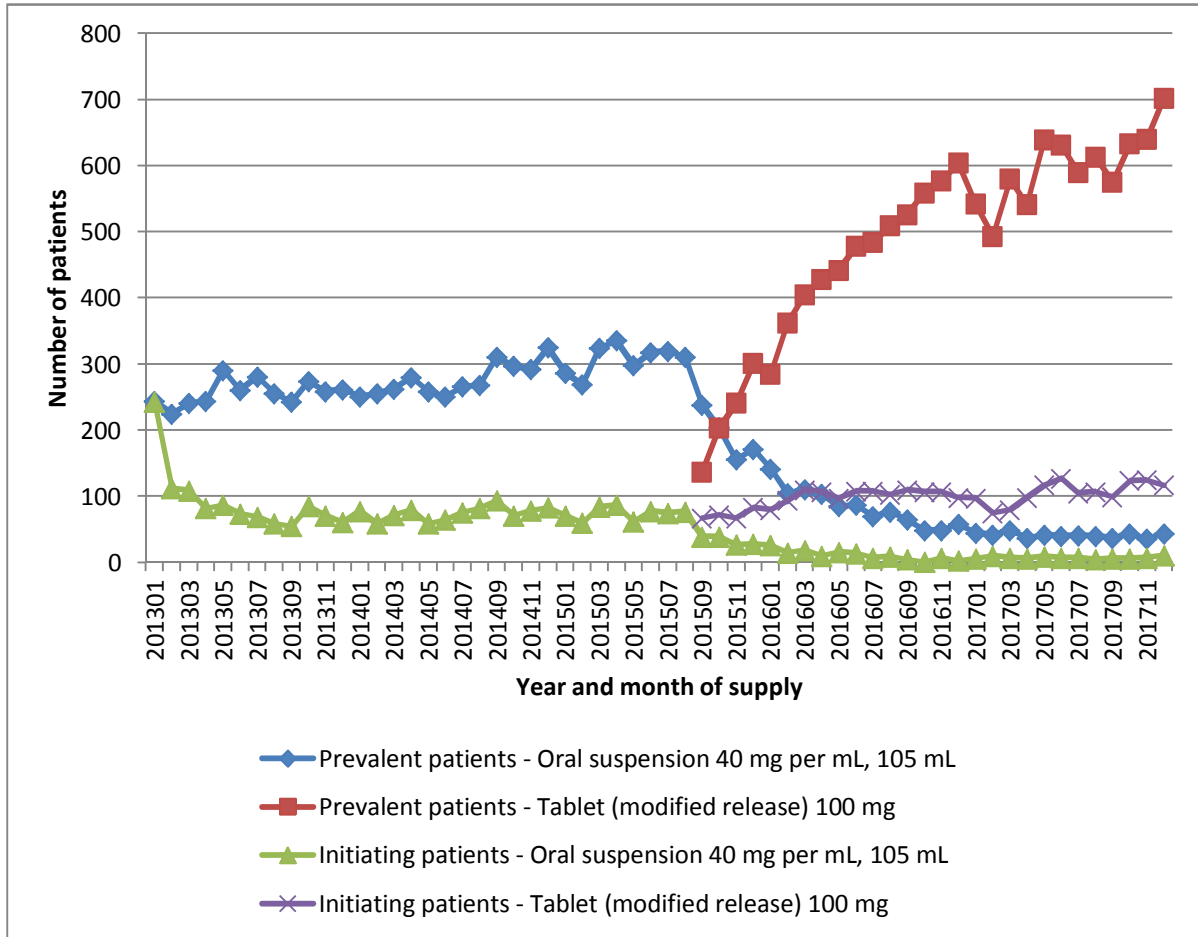


Figure 5: Number of prevalent and incident patients for posaconazole by form & strength

Source: DHS AAD, DHS supplied prescriptions database to 31 December 2017; extracted 13 March 2018.

The number of incident patients commencing posaconazole for any indication has increased. In the two years prior to the listing of the tablet form, an average of 73 patients commenced posaconazole each month. In the two years after the tablet listed this increased to 110 patients per month. The number of prevalent treated patients has increased dramatically and is mostly for patients receiving prophylaxis (Figure 6).

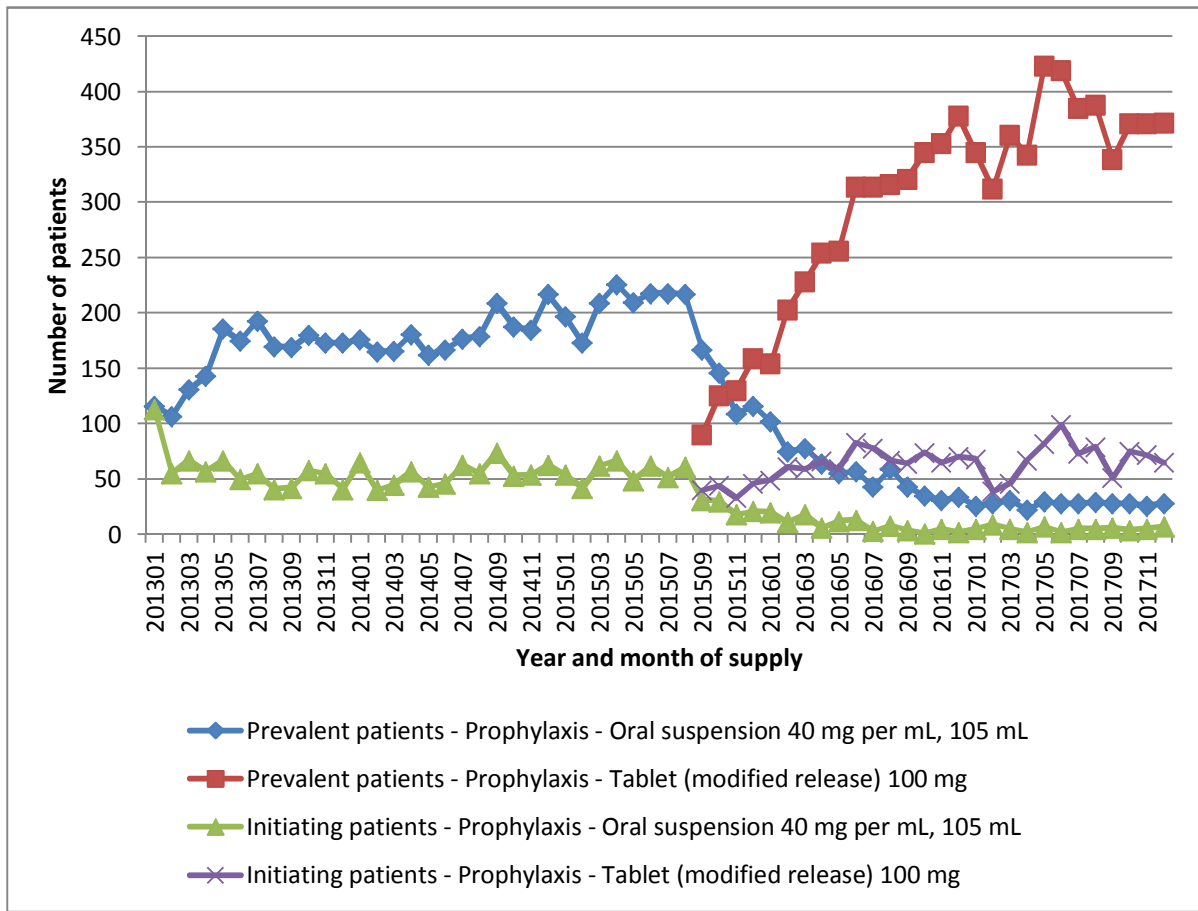


Figure 6: Prevalent and incident patients by form & strength for prophylaxis

Source: DHS, AAD DHS supplied prescriptions database to 31 December 2017; extracted 13 March 2018.

As a consequence of more new patients commencing treatment there are also more patients on treatment. However the magnitude of the increase in prevalent patients may be due to other changes in utilisation patterns such as adherence or duration on therapy. This is investigated further below.

Time to prescription refill

The PBAC anticipated that usage of posaconazole may increase due to ease of use of tablets over liquid. A time to refill analysis was undertaken to see if there were any major differences between the two formulations that might indicate different patterns of adherence. As a formal adherence analysis was not undertaken this analysis is indicative only.

Figure 7 presents the number of days to a patient’s next supply of a script for posaconazole stratified by form and strength for prophylaxis of invasive fungal infections. Figure 8 presents the same data for the treatment of aspergillosis.

The distribution of time to refill is similar for the two forms. The most common time to refill for both forms of posaconazole for prophylaxis and the treatment of aspergillosis is 28 days. Other peaks in refill times are seen at 7, 21, 35 and 42 days.

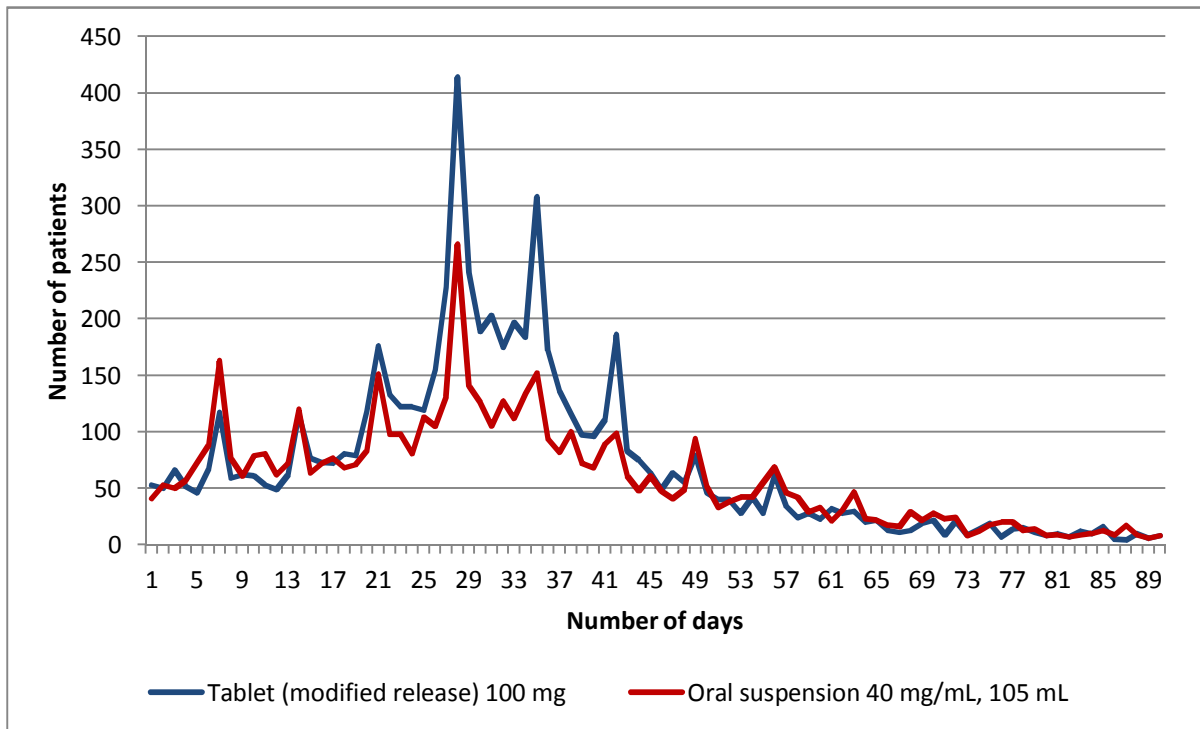


Figure 7: Time to refill analysis for posaconazole for prophylaxis

Data are presented by days to next supply.

Source: DHS AAD, DHS supplied prescriptions database to 31 December 2017; extracted 13 March 2018.

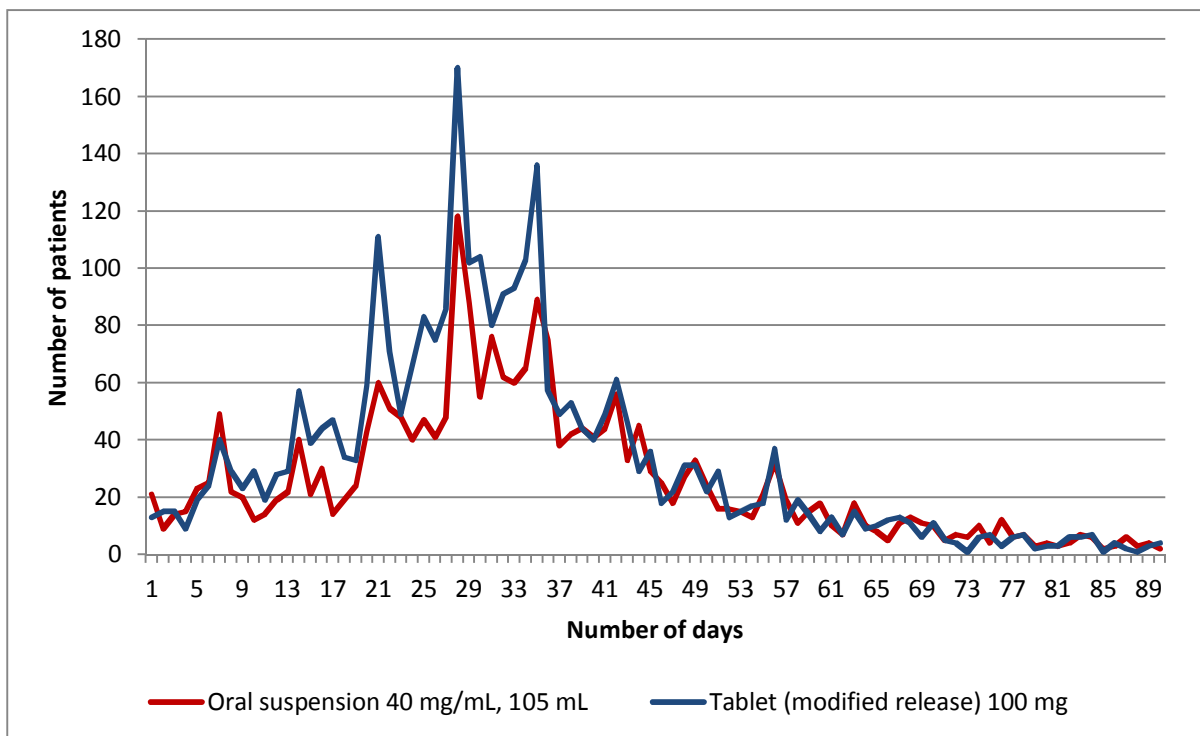


Figure 8: Time to refill analysis for posaconazole for aspergillosis

Data are presented by days to next supply. Indications were determined by authority codes from the Authority Approvals Database (AAD). Source: DHS AAD, DHS supplied prescriptions database to 31 December 2017; extracted 13 March 2018.

Duration on therapy

Length of treatment was estimated for 4 cohorts;

1. Patients who initiated posaconazole for prophylaxis in 2014. These patients did not initially have access to the tablet formulation which was listed in September 2015.
2. Patients who initiated posaconazole for prophylaxis in the 12 months, September 2015 to August 2016. These patients had access to the tablet formulation from their date of initiation.
3. Patients who initiated posaconazole for treatment (i.e. not prophylaxis) in 2014. These patients did not initially have access to the tablet formulation which was listed in September 2015.
4. Patients who initiated posaconazole for treatment (i.e. not prophylaxis) in the 12 months, September 2015 to August 2016. These patients had access to the tablet formulation from their date of initiation.

See methods section for more details.

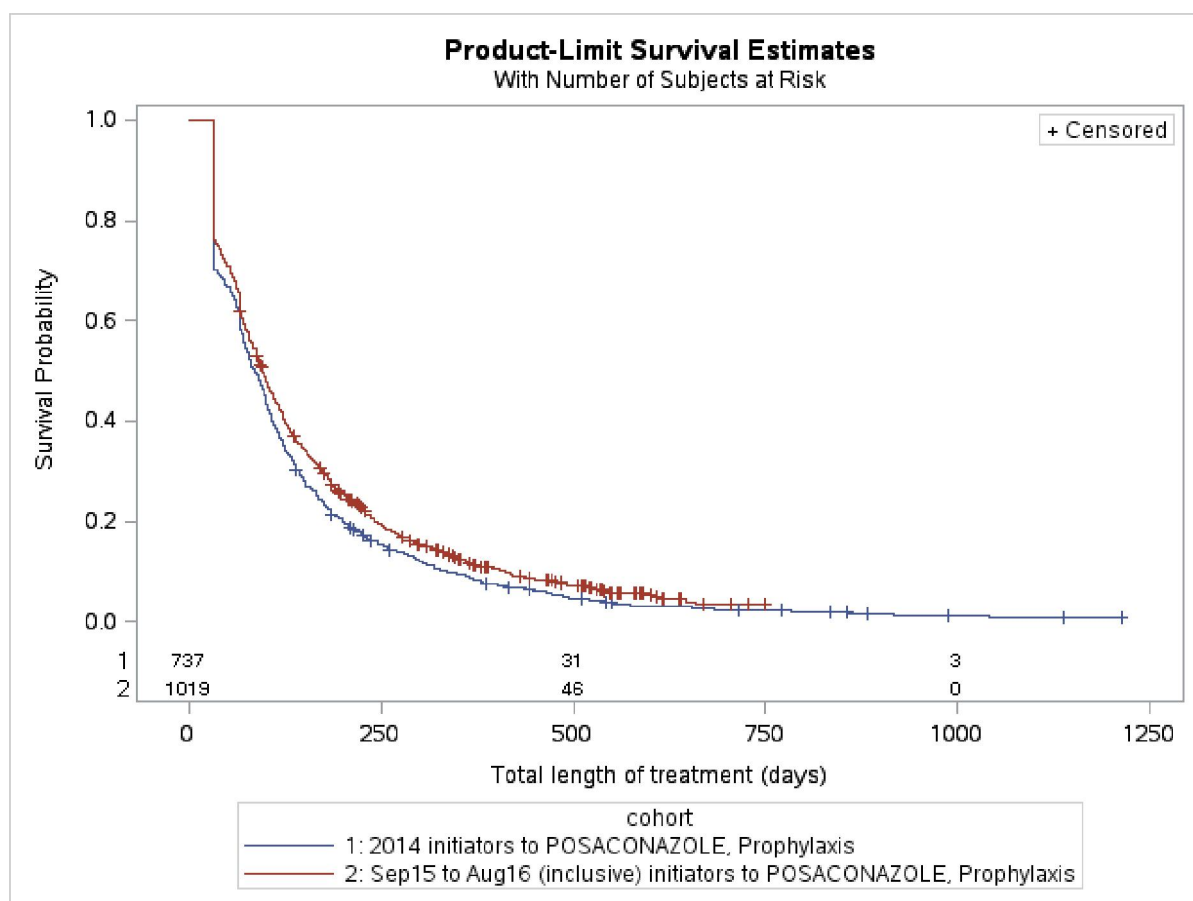


Figure 9: Length of treatment (excluding breaks) with posaconazole for prophylaxis by cohort

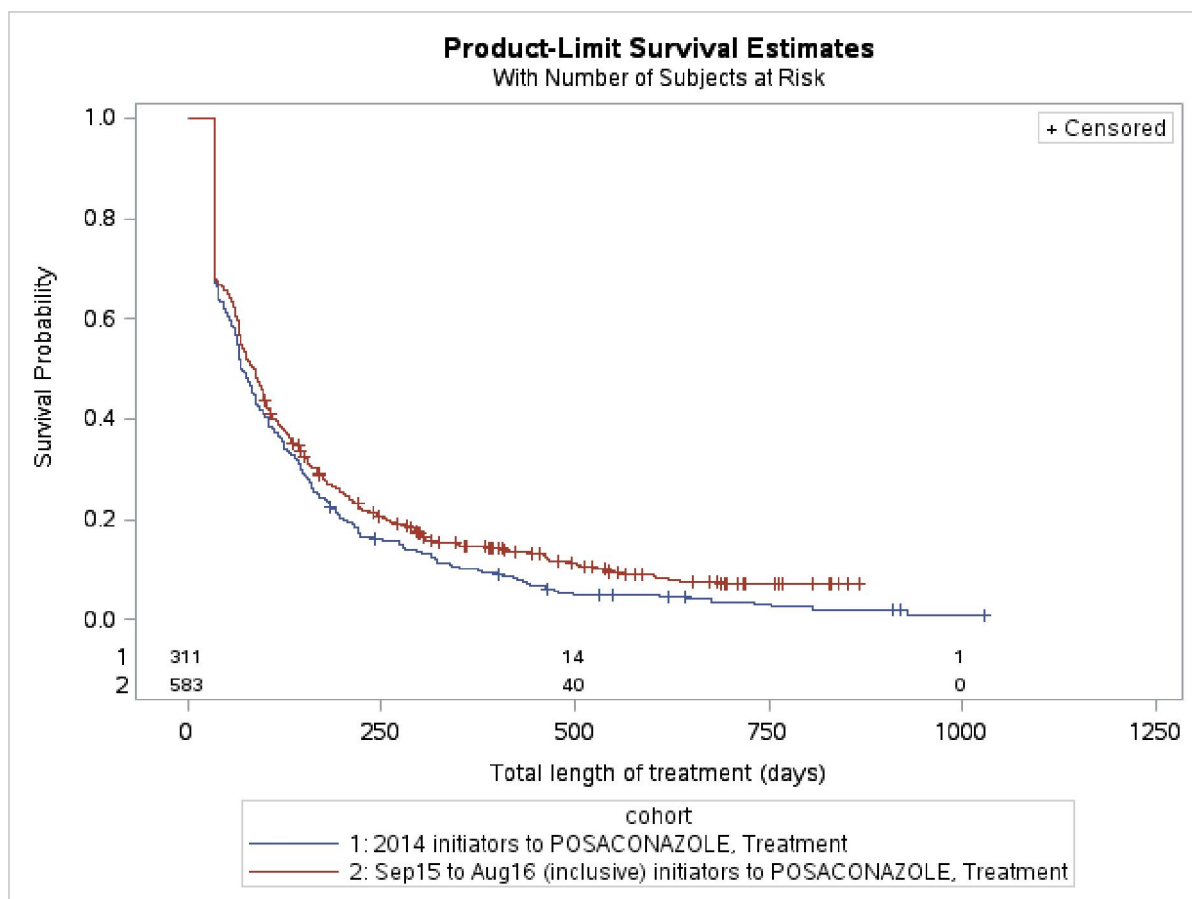


Figure 10: Length of treatment (excluding breaks) with posaconazole for treatment (i.e. not prophylaxis) by cohort

Table 3: Median length of treatment (excluding breaks)

Patient cohort	Median (Days)	Patients (n)
2014 initiators to posaconazole, prophylaxis	86	737
Sep 2015 to Aug16 initiators to posaconazole, prophylaxis	96	1019
2014 initiators to posaconazole, treatment	70	311
Sep 2015 to Aug16 initiators to posaconazole , treatment	84	583

There has been a modest increase in the length of treatment for both the prophylaxis and treatment following the availability of the tablet formulation.

Analysis of expenditure

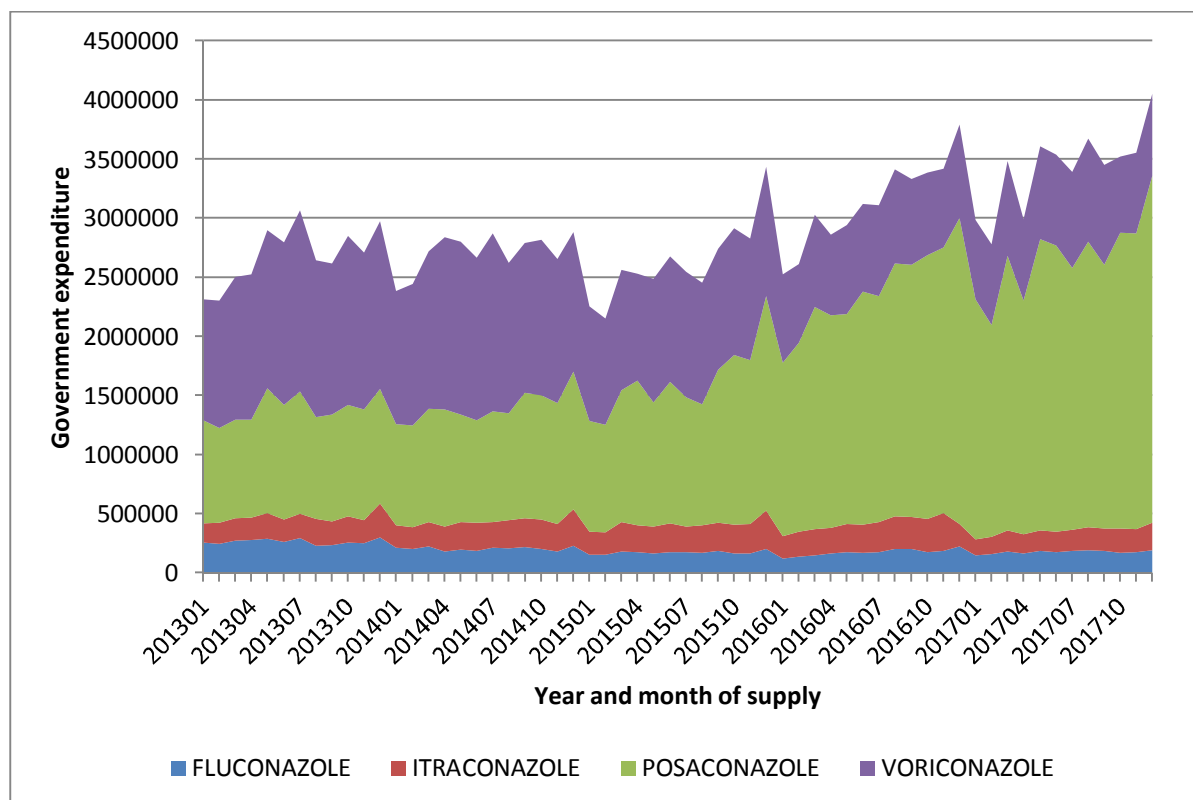


Figure 11: PBS benefits by for antifungal medicines

Source: DHS supplied prescriptions database to 31 December 2017; extracted 13 March 2018.

Figure 11 presents PBS benefits for posaconazole compared to fluconazole, itraconazole and voriconazole. The total benefits paid for posaconazole has seen a marked increase since the listing of the tablet form in September 2015. The cost of voriconazole decreased between December 2015 and February 2016, however has remained stable since then. The PBS benefits for itraconazole and fluconazole has remained low and stable since 1 January 2013. All of the medicines expect for posaconazole are subject to price disclosure reductions.

Analysis of actual versus predicted utilisation

A comparison of the predicted utilisation of posaconazole 100 mg modified release tablet from the minor submission verses actual use is shown in Table 4.

Table 4: Predicted versus actual use of posaconazole 100 mg modified release tablet

Parameter	Comparison	Year 1 (September 2015 – August 2016)	Year 2 (September 2016 – August 2017)
Overall posaconazole market			
Total number of posaconazole packs	Predicted units (P) ^a	████	████
	Actual packs (A) ^b	25,578	32,946
	% difference (A-P)/P	████	████
Posaconazole tablets			
Uptake of tablets within the posaconazole market (%)	Predicted units (P)	████	████
	Actual packs (A)	72%	92%
Number of packs of posaconazole tablets	Predicted units (P) ^a	████	████
	Actual packs (A)	18,476	30,456
	% difference (A-P)/P	████	████
PBS benefits for posaconazole tablets (less patient co-pay)	Predicted (P)	████████	████████
	Actual (A)	\$15,469,777	\$25,139,342
	% difference (A-P)/P	████	████

Source: Predicted values are from the minor submission for posaconazole tablets considered at the March 2015 PBAC meeting. Actual values from the DHS supplied prescriptions database to 31 Aug 2017; extracted 05 Mar 2018.

^aEquivalent packs of tablets. Includes a conversion factor based on the duration of therapy per pack of suspension and pack of tablets, and accounts for proportion of use for prophylaxis and treatment

The utilisation of posaconazole tablets was grossly underestimated because growth in the posaconazole market as a result of the listing of the tablet formulation was not accounted for and because the rate of uptake of the tablet formulation was underestimated.

Discussion

When recommending the listing of posaconazole tablets on the PBS the PBAC considered that usage is likely to increase due to the ease of use of tablets over the liquid, but considered it uncertain whether any additional patient benefit from such use would accrue. The analyses provided in this report confirm that the posaconazole market expanded significantly following the listing of the tablet formulation. Factors contributing to the

increased market include an increase in the number of new patients commencing treatment and prophylaxis as well as an increase in the median time on treatment.

The assessment of whether the increased use is clinically appropriate and within the PBS restrictions is limited by the available PBS data. For the treatment indications, PBS subsidy of posaconazole is restricted to patients who are unable to tolerate, or have disease refractory to, alternative therapy. The assessment of whether alternative treatment has been used prior to posaconazole is limited because many of the alternative therapies are not PBS listed (amphotericin B lipid complex, liposomal amphotericin B, caspofungin) and therefore not visible in the PBS data. In addition, therapies that are PBS listed but provided in a public hospital inpatient setting will also not be captured in PBS data. Further, the definition of 'intolerant to' alternative therapies is not defined and may be broadly interpreted given the adverse event profiles and monitoring requirements for other agents, particularly voriconazole.

For prophylaxis, posaconazole is subsidised for the two very high risk patient groups where there was clinical trial evidence of benefit, however guidelines recommend prophylaxis in some other high risk groups. Although use for prophylaxis can be distinguished from treatment in the PBS data by matching to the Authority approval indication, use for the two prophylaxis groups cannot be directly differentiated. An analysis of co-prescribed therapies (such as use of azacitidine to identify MDS or AML patients) could be undertaken if the DUSC and/or the PBAC consider it warranted. Clinical advice would be required on the range of PBS medicines that could identify MDS and AML patients, and whether patients without these medicines could be assumed to be AlloHSCT patients with GVHD. There may be challenges in assigning an indication for restricted benefit or unrestricted chemotherapy agents. The analysis of co-prescribed therapies may shed some light on use of posaconazole for non-PBS subsidised populations.

An increase in the duration on treatment with posaconazole was not unexpected given the ease of use of the tablets over the suspension. Optimal duration of prophylaxis and treatment is not clear. At the request of the PBAC, advice will be sought from the clinical experts responsible for the antifungal treatment guidelines to ascertain the most appropriate duration of therapy for both prophylaxis and treatment.

DUSC consideration

The analysis noted that uptake of the tablet formulation of posaconazole was rapid and there was a sharp decline in prescriptions for the oral liquid. The analysis also noted that the availability of the tablet formulation resulted in substantial growth in the overall use of posaconazole. The number of incident patients commencing posaconazole has increased. In the two years prior to the listing of the tablet form, an average of 73 patients commenced posaconazole each month. In the two years after the tablet was listed this increased to 110 patients per month. DUSC considered that the uptake of tablets was higher than expected.

The analysis showed that the number of prevalent treated patients has increased dramatically and is mostly for patients receiving prophylaxis. DUSC noted that there was an increase in the number of patients initiating posaconazole for treatment and prophylaxis

following the listing of posaconazole tablets, which was not accounted for in the submission. The sponsor response stated that the increase in the patient population using posaconazole on the PBS is attributable to posaconazole tablets being better tolerated and preferred over the oral solution, the improvement in diagnostic techniques for fungal infections, and an increased number of allogeneic haematopoietic stem cell transplants (HSCT) being performed in Australia. DUSC agreed with the sponsor that there is some evidence there is an increasing number of patients receiving allogeneic HSCT. DUSC noted that it is not possible to tell from the PBS data alone whether all of the increase in use of posaconazole was appropriate.

The analysis noted that a time to refill analysis shows similar time to dispensing of the tablet and the liquid form indicating that adherence may be similar for the two formulations. DUSC commented that there is a similar pattern evident for time to refill for the tablet and suspension for treatment and prophylaxis.

At the time of its recommendation, PBAC (March 2015) considered that duration of therapy was a significant source of uncertainty, and that there was a risk that patients would persist on treatment in the absence of clear additional clinical benefit. There has been a modest increase in the duration of treatment following the availability of the posaconazole tablet formulation with the median length of treatment for both the prophylaxis and treatment determined to be 96 and 84 days, respectively. DUSC considered that the median duration of therapy for prophylaxis was consistent with guidelines for graft versus host disease in allogeneic HSCT patients, but may be longer than expected for anticipated neutropenia post chemotherapy for acute myeloid leukaemia or myelodysplastic syndromes. The report noted that an analysis of co-prescribed therapies (such as use of azacitidine to identify MDS or AML patients) could be undertaken if the DUSC or the PBAC consider it warranted. Clinical advice would be required on the range of PBS medicines that could identify MDS and AML patients, and whether patients without these medicines could be assumed to be AlloHSCT patients with GVHD. There may be challenges in assigning an indication for restricted benefit or unrestricted chemotherapy agents. The analysis of co-prescribed therapies may shed some light on use of posaconazole for non-PBS subsidised populations. Although DUSC considered that such an analysis may shed some light on how posaconazole is being used in practice, overall DUSC did not think the analysis would be sufficiently definitive given that there are a number of different chemotherapy protocols for AML.

DUSC considered that the median duration for treatment is consistent with guidelines of invasive aspergillosis and fusariosis, although duration of treatment is dependent on patient response. The sponsor response stated that the estimated median duration of treatment with posaconazole is within the recommended guidelines for prophylaxis and treatment of fungal infections. The sponsor response also noted that duration of treatment with posaconazole tablets may be longer than the duration of treatment with posaconazole oral solution due to ease of use, allowing patients to fully complete their treatment regime. DUSC noted that the Australasian Society of Infectious Diseases has been requested to provide advice on the appropriate duration of therapy for both treatment and prophylaxis prior to the PBAC meeting.

DUSC commented that it is difficult to assess if use of posaconazole in the treatment indication is appropriate. The analysis noted that for the treatment indications, PBS subsidy of posaconazole is restricted to patients who are unable to tolerate or have disease refractory to alternative therapy. The assessment of whether alternative treatment has been used prior to posaconazole is limited because many of the alternative therapies are not PBS listed (amphotericin B lipid complex, liposomal amphotericin B, caspofungin) and therefore not visible in the PBS data. In addition, therapies that are PBS listed but provided in a public hospital inpatient setting will also not be captured in PBS data. Further, the definition of 'intolerant to' alternative therapies is not defined and may be broadly interpreted given the adverse event profiles and monitoring requirements. The sponsor response stated that the definition of 'intolerant to' should remain broadly interpreted, as there are a multitude of reasons for which a patient may be discontinued from using other agents for the treatment of fungal infections. The sponsor was of the view that it would be inappropriate to restrict the definition of "unable to tolerate" in order to further restrict use of posaconazole, as clinician judgement is sufficient in this high risk patient population.

The analysis noted that the utilisation of posaconazole tablets was substantially underestimated. The analysis suggested that the underestimation is due to growth in the posaconazole market as a result of the tablet formulation listing not being accounted for, and because the rate of uptake of the tablet formulation was underestimated. DUSC commented that the posaconazole market has expanded substantially following the listing of the tablet formulation. [REDACTED]

The sponsor agreed with the analysis that the increased utilisation of posaconazole tablets is likely to be due to an increase in the number of patients receiving treatment and prophylaxis, as well as a modest increase in the median time on treatment. The sponsor response stated that risk of uncertainty when listing posaconazole has been managed by a Risk Sharing Agreement (RSA) between Merck Sharp and Dohme (MSD) and the government and noted that government expenditure associated with increased utilisation has not increased to the same degree.

The use of posaconazole for treatment of 'other' fungal infection indications in the second half of 2017 increased sharply (Figure 2 of the report). DUSC also noted that the most recent three data points (Oct-Dec 2017) showed a trend of increasing utilisation of fluconazole (Appendix B). There is often a seasonal increase in prescription volume at the end of the calendar year due to the effect of the safety net. DUSC requested that use of these medicines be monitored to see if there is a continuing trend of increased utilisation.

DUSC actions

- 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

Merck Sharp and Dohme Pty Ltd: 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 A

There are currently four azole antifungal medicines listed on the PBS: fluconazole, itraconazole, posaconazole and voriconazole. Of the currently listed azole antifungal medicines, only voriconazole and posaconazole are listed for prophylaxis.

A summary of PBS restrictions is provided below for voriconazole, itraconazole and fluconazole. For full details of the current PBS listing refer to the PBS website.

Fluconazole is a restricted benefit for:

- Cryptococcal meningitis
- Maintenance therapy of cryptococcal meningitis in immunosuppressed patients
- Oropharyngeal and oesophageal candidiasis in immunosuppressed patients
- Prophylaxis of oropharyngeal candidiasis in immunosuppressed patients
- Serious or life-threatening Candida infections

Itraconazole is a restricted benefit for:

- Systemic aspergillosis, Systemic sporotrichosis & Systemic histoplasmosis
- Treatment and maintenance therapy of disseminated pulmonary histoplasmosis infection in patients with AIDS
- Treatment and maintenance therapy of chronic pulmonary histoplasmosis infection in patients with AIDS
- Oropharyngeal and oesophageal candidiasis in immunosuppressed patients.

Voriconazole is an authority required benefit for treatment and maintenance therapy of the following:

- Definite or probable invasive aspergillosis in immunocompromised patients
- 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
- Serious invasive mycosis infections (other than invasive aspergillosis).

Voriconazole is also listed for prophylaxis of invasive fungal infections including both yeasts and moulds in the following patient groups:

- at high risk of developing an invasive fungal infection due to anticipated neutropenia (an absolute neutrophil count less than 500 cells per cubic millimetre) for at least 10 days whilst receiving chemotherapy for acute myeloid leukaemia or myelodysplastic syndrome; OR
- at high risk of developing an invasive fungal infection due to having acute graft versus host disease (GVHD) grade II, III or IV, or, extensive chronic GVHD, whilst receiving intensive immunosuppressive therapy after allogeneic haematopoietic stem cell transplant; OR
- undergoing allogeneic haematopoietic stem cell transplant using either bone marrow from an unrelated donor or umbilical cord blood (related or unrelated),

and, be considered to be at high risk of developing an invasive fungal infection during the neutropenic phase prior to engraftment.

- A note to the restriction allows patients with graft versus host disease, acute myeloid leukaemia or myelodysplastic syndrome, applications for an increased maximum quantity to allow for up to 1 month's treatment and repeats sufficient for up to 6 months' treatment to be authorised.
- For patients undergoing allogeneic haematopoietic stem cell transplant, applications for an increased maximum quantity to allow for up to 1 month's treatment and repeats sufficient for up to 2 months' treatment may be authorised.

Appendix B

The number of PBS prescriptions for azole antifungal medicines for any indication is provided in Figure B.1. Topical formulations are excluded.

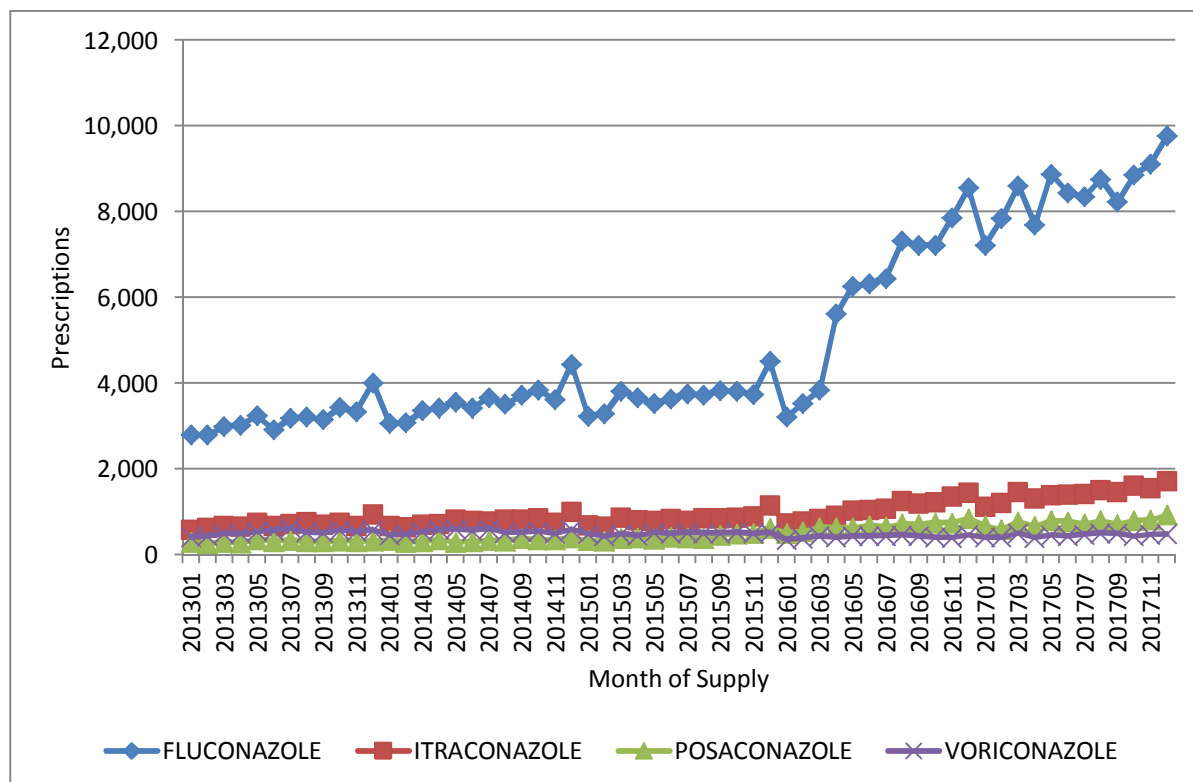


Figure B.1: PBS prescriptions of azole antifungal medicines (excluding topical)

Source: DHS supplied prescriptions database; extracted 09 March 2018.

The high and increasing utilisation of fluconazole has been considered in detail recently by the DUSC and PBAC and is not reconsidered here. For details of the DUSC consideration of antifungals for systemic use refer to the Public Release Document from the September 2016 DUSC meeting and the PBAC outcomes for March 2018.

In Figure B.2 fluconazole and itraconazole are removed so that changes in the use of posaconazole and voriconazole can be seen more clearly.

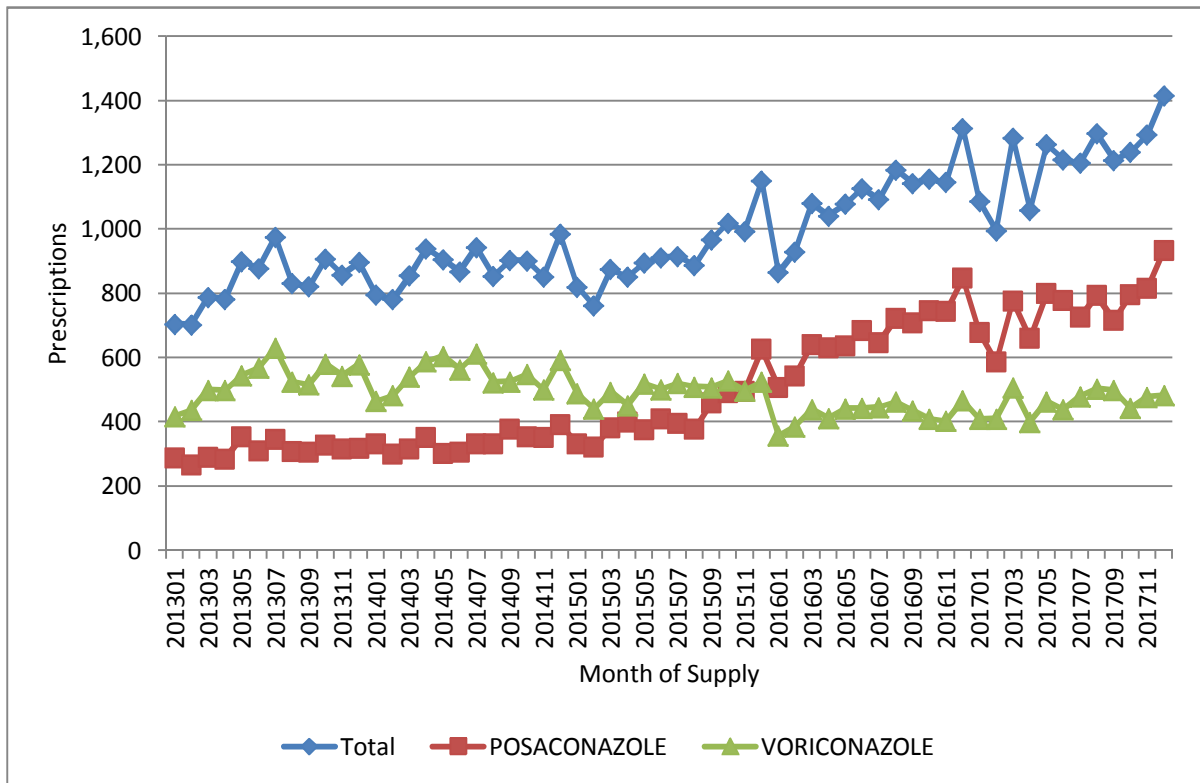


Figure B.2: Prescriptions of posaconazole and voriconazole

Source: DHS supplied prescriptions database; extracted 09 March 2018.