

Testosterone: utilisation analysis

Drug utilisation sub-committee (DUSC)

September 2016

Abstract

Purpose

The Pharmaceutical Benefits Advisory Committee (PBAC) requested a 12 month utilisation analysis of testosterone to assess the impact of a change in the restriction that occurred 1 April 2015. The change included involving a specialist in the treatment for all patients; amending the serum testosterone threshold for androgen deficiency in males who do not have established pituitary or testicular disorder; and excluding treatment for low serum testosterone due primarily to age, obesity, cardiovascular diseases, infertility or drugs.

The additional requirement to involve a specialist in treatment was the only change to the subsidy criteria for micropenis, pubertal induction, or constitutional delay of growth or puberty; or for androgen deficiency with established pituitary or testicular disorders.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

There are a variety of listings and forms of testosterone on the PBS. The first was listed prior to 1966.

Data Source / methodology

Data were extracted from the DUSC and Department of Human Services (DHS) prescription databases from the earliest available data and continuing to March 2016.

Key Findings

- The restriction change to testosterone on 1 April 2015 reduced the use of testosterone subsidised on the PBS and Repatriation Pharmaceutical Benefits Scheme (RPBS).
- In the year after the restriction change compared to the year before:
 - The number of patients initiating testosterone therapy was 60% lower.
 - There was an 86% reduction in patients initiating testosterone under the non-established androgen deficiency restriction.
 - There was a reduction in the rate of people 40 years and over starting testosterone.
 - The number of prevalent patients was 20% lower.
 - The number of initiating patients where the first prescription was written by a GP reduced by 80%.

- In 2015, the total number of supplied R/PBS-subsidised testosterone prescriptions was 17% less than in 2014. In 2015, Government expenditure in 2015 was \$16.2 million, down 20% from 2014.

Purpose of analysis

The Pharmaceutical Benefits Advisory Committee (PBAC) requested a 12 month utilisation analysis of testosterone to assess the impact of a change in the restriction that occurred 1 April 2015. The change included involving a specialist in the treatment for all patients; amending the serum testosterone threshold for androgen deficiency in males who do not have established pituitary or testicular disorder, and excluding treatment for low serum testosterone due primarily to age, obesity, cardiovascular diseases, infertility or drugs.

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Background

Previous reviews by DUSC

At its June 2012 meeting, DUSC noted a recently published research article highlighted an increase in PBS-subsidised testosterone prescribing. DUSC considered it timely to review the utilisation of testosterone and requested a report be prepared for consideration at its October 2012 meeting. The key findings of the report were:

- Utilisation of PBS-subsidised testosterone had doubled over the years 2007 to 2011.
- The listing of two products, testosterone transdermal gel and intramuscular injection 1000 mg, had driven the growth in the market.
- There was a trend towards more GPs initiating therapy than specialists.
- In 2011, Government expenditure for testosterone preparations was \$14.6 million, up from \$5.6 million in 2005. This was a growth of 260% over 5 years.
- Most initiations were for patients aged 40-79 years.

With regard to the testosterone PBS restrictions, DUSC was concerned that a high degree of variability had been observed in measurement of testosterone levels depending on the assay methodology adopted. DUSC suggested that the PBAC should review the testosterone restrictions and consider input from the various stakeholders.

For details of the DUSC consideration of testosterone, refer to the [Public Release Document](#) from the October 2012 DUSC meeting.

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

The findings from the DUSC October 2012 meeting were presented to the PBAC at the August 2013 Special PBAC meeting to consider if the PBS restrictions for testosterone products required revision.

The PBAC noted that the number of subsidised prescriptions increased, while non-PBS prescriptions had remained stable and low. Though the proportion of GPs writing the first testosterone prescription for a patient had increased only slightly (62% in 2005 to 68% in 2011), the PBAC noted that almost all of the growth in new patients treated in the most recent year of analysis (2011) was due to initiations by GPs (84%), rather than by specialists.

The PBAC noted the utilisation in the younger age groups had remained constant, while initiations for patients aged 40-79 years had increased over time. The PBAC considered that the growth in initiations for patients in the 40-79 aged cohorts may have been due to the increase in diagnosis and treatment of PBS listed indications; however, may also include inappropriate use outside the PBS restrictions, such as patients without a pathologically-based androgen deficiency.

The PBAC noted the original serum testosterone threshold was 8 nmol/L and was based on informed judgement from advice and correspondence from the Endocrine Society, the Australasian Paediatric Endocrine Group, sponsors at the time (Schering, Organon) and clinicians during the December 1998 and March 1999 PBAC meeting. The PBAC noted this threshold was vindicated in recent studies.

The PBAC acknowledged the concern raised by DUSC that a high degree of variability had been observed in the measurement of testosterone levels depending on the assay methodology used. The PBAC noted the challenges in clinical diagnosis of testosterone deficiency and the accuracy in establishing a definitive threshold.

Therefore, the PBAC recommended:

- Amending the serum testosterone threshold in the PBS restriction for men aged 40 years or older who do not have established pituitary disorders to 6-15 nmol/L in combination with a high LH (greater than 1.5 times the upper limit of the eugonadal reference range for young men, or greater than 14 IU/L, whichever is higher).
- Confirmation of androgen deficiency should include measurement of serum testosterone, LH and FSH to allow for the appropriate diagnosis of primary androgen deficiency. (The PBAC noted that testing of serum LH and FSH together with serum testosterone is not expected to increase the cost to the Commonwealth as the MBS item 66695 already covers up to 6 assays from a single sample.)
- Patients prescribed testosterone must be treated by or in consultation with a specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine or have an appointment to be assessed by one of these specialists.
- Excluding treatment for low serum testosterone due primarily to age, obesity, cardiovascular diseases, infertility or drugs. These indications had not been assessed for efficacy and cost-effectiveness by the PBAC.

The PBAC recommended that a review of testosterone utilisation by DUSC be undertaken twelve months after the PBS restriction has been finalised and implemented.

For further details refer to the [Public Summary Document](#) from the August 2013 Special PBAC meeting.

At the July 2014 PBAC meeting, the PBAC was advised of responses from sponsors and stakeholders in relation to recommended amendments to the PBS restrictions for testosterone products from the August 2013 Special PBAC meeting. Following stakeholder consultation, the Secretariat undertook a further review of the proposed amendments to the restrictions and considered that they did not accurately reflect the intent of the PBAC.

The PBAC recommended amending the restrictions for testosterone products:

- For restrictions for androgen deficiency, remove redundant reference to the condition not being due to age, obesity, cardiovascular diseases, infertility or drugs;
- To include registered members of the Australasian Chapter of Sexual Health Medicine as prescribers that are able to prescribe testosterone products on the PBS.

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

At its July 2015 meeting, the PBAC recommended amending the restriction wording for testosterone to remove the population criterion 'patient must be male' as per a minor submission to enable access by transgender and intersex patients.

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

PBS listing details (as at August 2016)

Below are the R/PBS listings of testosterone products as at August 2016.

Table 1: R/PBS listing of testosterone

| Item | Name, form & strength, pack size | Max. quant. | Rpts | DPMQ | Brand name and manufacturer |
|-------------|---|--------------------|-------------|-------------|--|
| 2114G | Testosterone enanthate 250 mg/mL injection, 3 x 1 mL syringes | 1 | 3 | \$32.91 | Primoteston® Bayer Australia Ltd |
| 10205D | Testosterone undecanoate 1 g/4 mL injection, 4 mL vial | 1 | 1 | \$132.33 | Reandron® Bayer Australia Ltd |
| 2115H | Testosterone undecanoate 40 mg capsule, 60 | 1 | 5 | \$36.26 | Andriol Testocaps® Merck Sharp & Dohme Pty Ltd |
| 10380H | Testosterone 1% (12.5 mg/actuation) gel, 2 x 60 actuations | 1 | 4 | \$87.17 | Testogel® Besins Healthcare Australia Pty Ltd |
| 8830R | Testosterone 1% (50 mg/5 g) gel, 30 x 5 g sachets | 1 | 5 | \$87.17 | Testogel® Besins Healthcare Australia Pty Ltd |

| | | | | | |
|--------|---|---|---|---------|--|
| 2341F | Testosterone 2% (30 mg/actuation) solution, 60 actuations | 1 | 5 | \$76.23 | Axiron® Eli Lilly Australia Pty Ltd |
| 10378F | Testosterone 5% (50 mg/mL) cream, 50 mL | 1 | 6 | \$73.42 | Androforte® Lawley Pharmaceuticals Pty Ltd |
| 8460G | Testosterone 2.5 mg/24 hours patch, 60 | 1 | 5 | \$87.78 | Androderm® Allergan Australia Pty Ltd |
| 8619P | Testosterone 5 mg/24 hours patch, 30 | 1 | 5 | \$87.78 | Androderm® Allergan Australia Pty Ltd |

Source: the [PBS website](#).

Restriction

All the testosterone items in the above table are PBS-listed for androgen deficiency, micropenis, pubertal induction and the delay in growth or onset of puberty. For a list of restriction codes for the classical androgen deficiencies, refer to Appendix A.

For both classical and non-classical androgen deficiencies, a telephone authority approval must be obtained by the prescriber from the Department of Human Services. The level of approval was not altered by the change to the PBS restriction that occurred on 1 April 2015.

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

PBS Restriction (abridged) for testosterone before and after the change

The following table outlines the abridged restriction before and after the restriction change occurred. On 1 October 2015, the restriction was changed to remove the term 'males' from the restriction. The current restriction in Table 2 includes all changes made to the restriction on and after 1 April 2015.

Table 2: Restriction before and after the restriction change

| Prior to April 2015 | Current |
|---|--|
| <p>Androgen deficiency</p> <ul style="list-style-type: none"> in males 40 years or older who do not have established pituitary or testicular disorders other than aging <p>• confirmed by at least 2 morning blood samples taken on different mornings.</p> <p>• defined as</p> <p>(i) testosterone less than 8 nmol per L;</p> <p>OR</p> <p>(ii) testosterone 8-15 nmol per L with high luteinising hormone (LH) (greater than 1.5 times the upper limit of the eugonadal reference range for young men)</p> | <p>Androgen deficiency</p> <ul style="list-style-type: none"> in patients 40 years or older who do not have established pituitary or testicular disorders and the condition must not be due to age, obesity, cardiovascular diseases, infertility or drugs. <p>• confirmed by at least 2 morning blood samples taken on different mornings.</p> <p>• defined as</p> <p>(i) testosterone less than 6 nmol per L;</p> <p>OR</p> <p>(ii) testosterone between 6 and 15 nmol per L with greater than 1.5 times the upper limit of the eugonadal reference range for young men, or greater than 14IU per L, whichever is higher)</p> <p>• treated by, in consultation with, or have appointment to see specified specialists.</p> |

Date of listing on PBS

- Testosterone esters injection (delisted January 2012): pre-1966
- Testosterone enanthate injection: pre-1974
- Testosterone undecanoate capsule: April 1990
- Testosterone subcutaneous implant: November 1996
- Testosterone transdermal patch: November 2000
- Testosterone transdermal gel: August 2005
- Testosterone undecanoate injection: August 2006
- Testosterone transdermal solution: March 2013
- Testosterone transdermal cream: August 2015

Changes to listing

For changes to R/PBS listing, refer to Appendix B. Current PBS listing details are available from the [PBS website](#).

Dosage and administration

A wide range of products are registered in Australia for use as testosterone replacement therapy. Gel, cream, liquid and patch formulations are generally applied daily; capsules are usually taken twice daily; shorter acting intramuscular (IM) injections given every 2-3 weeks; and longer acting IM injections every 10-14 weeks.

Further information is provided in Appendix C, [the Product Information](#) and [the Consumer Medicines Information](#).

Clinical situation

Hypogonadism is a disorder that results in the testes being unable to produce both physiological levels of testosterone (androgen deficiency) and adequate numbers of functional sperm for paternity (male infertility). Most often, hypogonadism is due to congenital or acquired defects of the testes (primary testicular failure). The delay in growth or onset of puberty, micropenis and pubertal induction are examples of primary testicular failure (classical early onset testosterone deficiencies).¹

There are a variety of Australian and international position and consensus statements regarding testosterone treatment. The Endocrine Society of Australia (ESA) recently published a position statement¹ including indications for testosterone therapy. The position statement recommends testosterone treatment for androgen-deficient men with proven pathological hypogonadism, regardless of age. The position statement also notes that there are limited data from high-quality randomised controlled trials with clinically meaningful

¹ Yeap et al. Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy. Med J Aust 2016; 205(4): 173-179. DOI: 10.5694/mja16.00393.

outcomes to justify testosterone treatment in older men without hypothalamic, pituitary or testicular disease.

In addition, the ESA position statement notes that obesity, metabolic syndrome and type 2 diabetes are associated with lowering of circulating testosterone levels but without elevation of LH and FSH levels. Evidence of safety and efficacy of treatment with testosterone in this setting is lacking. There is a clinical trial being conducted in Australia (recruiting from 2013 to 2016) studying the effects of testosterone therapy and lifestyle modification on diabetes prevention. It aims to recruit 1,500 men across Australia for a two year period.²

Methods

The analyses used data from the DUSC database and the Department of Human Services (DHS) supplied prescriptions database.

The DUSC database combines data on PBS prescriptions submitted to the Department of Human Services (DHS) for payment of an R/PBS 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. Testosterone enanthate injection and testosterone undecanoate are priced under the general patient copayment. The DUSC database includes an estimate of private prescriptions based on dispensing data from a sample of pharmacies to the end of August 2012. An estimate of private prescriptions is not included from 1 September 2012. The DUSC database was used for analyses of prescriptions and R/PBS benefits.

The DHS supplied prescriptions database includes data submitted to DHS for payment of an R/PBS subsidy by the Government. This database includes actual under co-payment prescription data from 1 April 2012. Patient counts were based on de-identified unique patient identification numbers (PINs) from the prescription data. This allows for patients to be classified as new patients and to identify prior treatments. The DHS supplied prescriptions database was used for patient level analyses; including age, prescriber type and tracking original prescription supplies.

For the patient level analyses, patients initiating to therapy were defined as those who have not been supplied testosterone since April 2003. Age was assigned based on the first supply in the time period.

An analysis of testosterone initiators by age was conducted for three years before and one year after the restriction change. The number of initiating patients in each age bracket was determined from the DHS supplied prescriptions database. These were then standardised by the male Australian population according to the Australian Bureau of Statistics (ABS) Quarterly Population Estimates (ERP), by State/Territory, Sex and Age database in

² T4DM Clinical Trial. Information available at: <http://www.t4dm.org.au/>

September 2015. The rates of patients initiating on testosterone were calculated as the number of initiating patients divided by the male ABS Estimated Residential Population (ERP) population³ in the specific year of each initiating cohort (as at 30 June). The rates are expressed as the number of incident patients per 100,000. The age adjusted rates were derived using the Direct Method.⁴

A patient level analysis of original prescriptions was conducted. Original prescriptions are an indication of patient contact with a doctor and as such may be an indicator of prescriber intent. Patients who were supplied an original prescription for testosterone in the year before the restriction change (April 2014 to March 2015) were followed in the data to determine whether they received a subsequent original prescription in the year following the restriction change (April 2015 to March 2016). For comparison, this same process was completed for patients supplied an original prescription in April 2013 to March 2014 (two years before the restriction change) who were followed up in April 2014 to March 2015. This analysis was performed as a proxy for patients discontinuing R/PBS-subsidised testosterone.

Aggregated data on Authority approvals and rejections was provided by the Department of Human Services. It covered the period from January 2015 to June 2016.

Private prescription data was provided by MedicineInsight for the period January 2014 to June 2016. They compared the number of original and repeat prescriptions ordered by 364 MedicineInsight general practices in the 15 months prior to 1 April 2015 and those ordered in the 15 months after.

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.⁵ The publicly available DHS Medicare data only includes subsidised R/PBS prescriptions with prescriptions under the patient co-payment not included.

Limitations of the data

For interpreting the results of this analysis, it should be noted that prescriptions for testosterone are valid for 12 months from the date of prescribing. Therefore, in the 12 months after the restriction change, there are prescriptions included that are valid but may not comply with the new PBS restriction. Further, only 12 months of data since the change in restriction was available at the time of the analysis.

³ Quarterly Population Estimates (ERP), by State/Territory, Sex and Age, extracted. The data was sourced from the ABS at <http://stat.abs.gov.au/>

⁴ [Principles on the use of direct age-standardisation in administrative data collections](#), September 2011, AIHW

⁵ 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

Figure 1 depicts the number of testosterone prescriptions supplied from January 2006 to 30 April 2016.

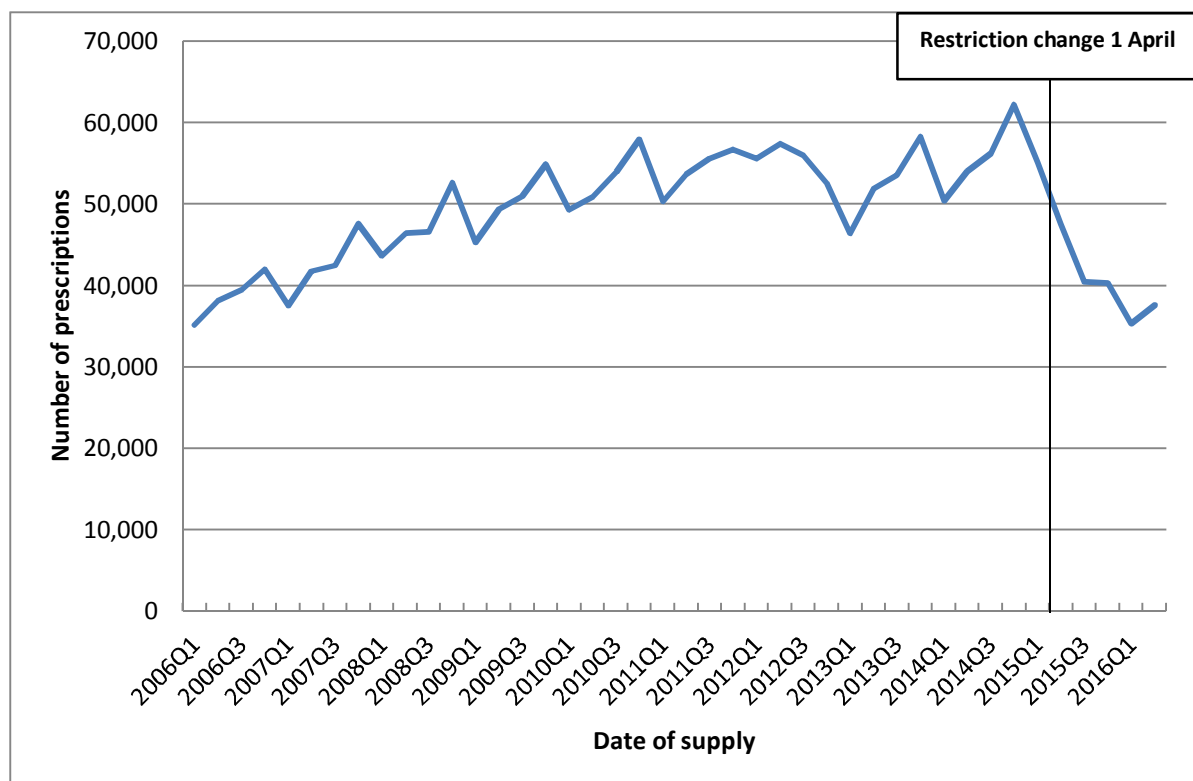


Figure 1: Testosterone prescriptions supplied per quarter from January 2006 to 30 June 2016

Prescriptions by date of supply. Includes under co-payment estimate to March 2012 and actual data from April 2012. Private estimate until August 2012. Source: DUSC database accessed August 2016.

The total number of testosterone prescriptions supplied increased steadily from quarter one 2006 (n=35,173) to quarter four 2014 (n=62,241). The trajectory of growth in testosterone prescriptions can be seen from January 2006 up until the time of the restriction change. At that point, a downwards trend can be seen.

Table 3 contains the number of prescriptions supplied on the R/PBS each year from 2013 to 2016.

Table 3: Number of R/PBS testosterone prescriptions supplied

| Year | Number of prescriptions | Annual Growth |
|-------------------|-------------------------|---------------|
| 2012 | 189,895 | N/A |
| 2013 | 210,243 | 10.7% |
| 2014 | 222,955 | 6.0% |
| 2015 | 183,745 | -17.6% |
| 2016 [†] | 72,918 | N/A |

[†] Part year (1 January to 30 June)

Prescriptions by date of supply. Includes under co-payment estimate and actual.

Source: DUSC database accessed August 2016

In 2015, the total number of R/PBS subsidised prescriptions supplied was 17.6% less than the year before.

Analysis of expenditure

Table 4 contains the R/PBS benefits and the growth rates in R/PBS prescriptions and benefits for testosterone.

Table 4: R/PBS benefits for testosterone

| Year | Total | Annual Growth |
|-------------------|--------------|---------------|
| 2012 | \$17,016,211 | N/A |
| 2013 | \$18,784,084 | 10.4% |
| 2014 | \$20,205,906 | 7.6% |
| 2015 | \$16,226,386 | -20% |
| 2016 ^a | \$6,289,683 | N/A |

^a Part year (1 January to 30 June)

Source: DUSC database using date of supply, which may be slightly different to publicly available Medicare Australia date of processing data, accessed August 2015.

The reduction in benefits paid in 2015, compared with 2014, is consistent with the reduction in prescription numbers.

Figure 2 shows the number of testosterone prescriptions supplied on the R/PBS from October 2012 to 31 March 2016 by individual testosterone items.

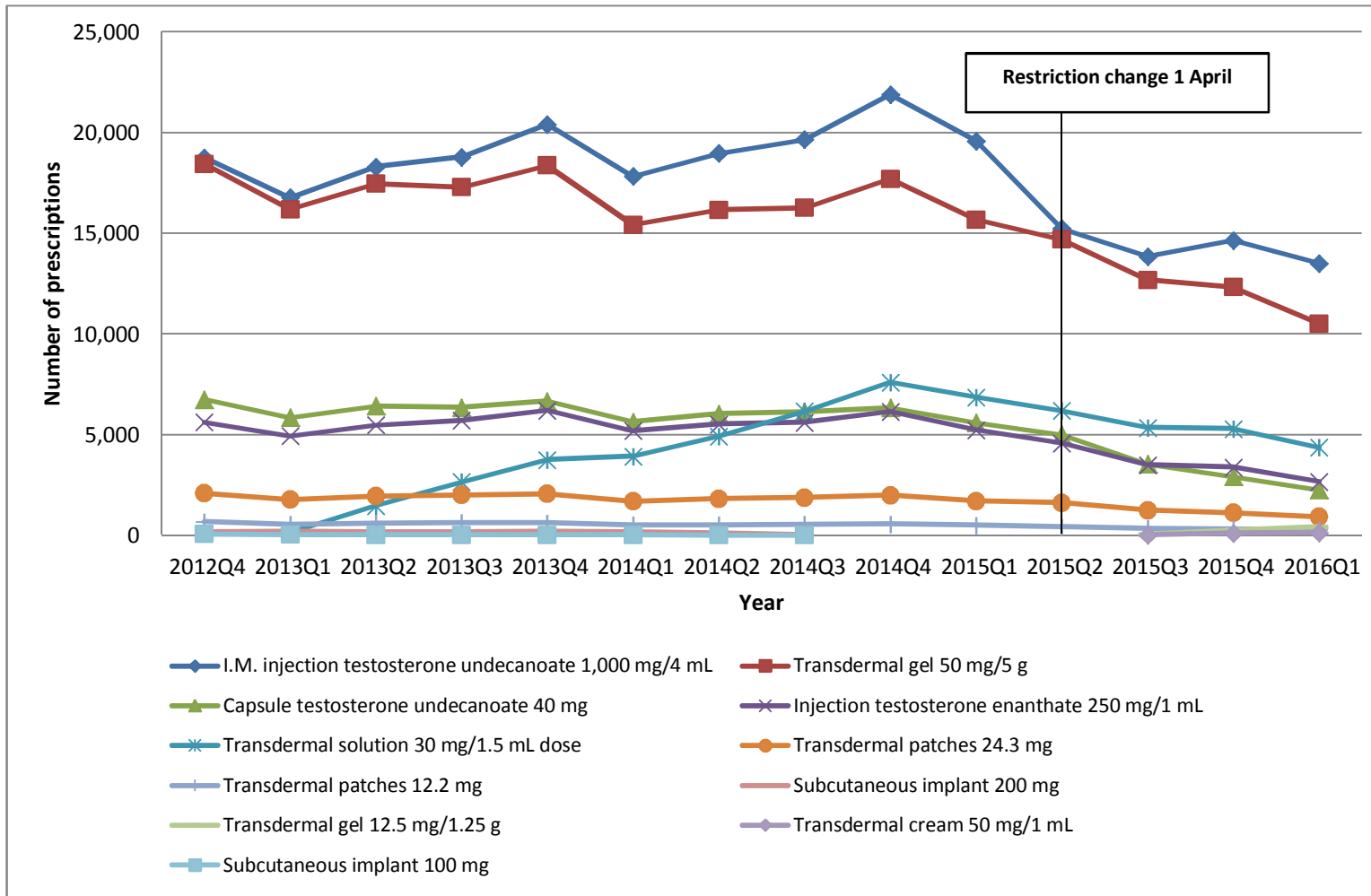


Figure 2: R/PBS supplied testosterone prescriptions by formulation and date of supply

Prescriptions by date of supply. Source: DUSC database accessed July 2016.

Figure 2 illustrates that the intramuscular undecanoate and transdermal gel were the two most frequently supplied testosterone forms.

Patients initiating and prevalent to therapy

Figure 3 depicts the number of patients supplied their first testosterone prescription and prevalent patients supplied a prescription by years surrounding the restriction change on 1 April 2015.

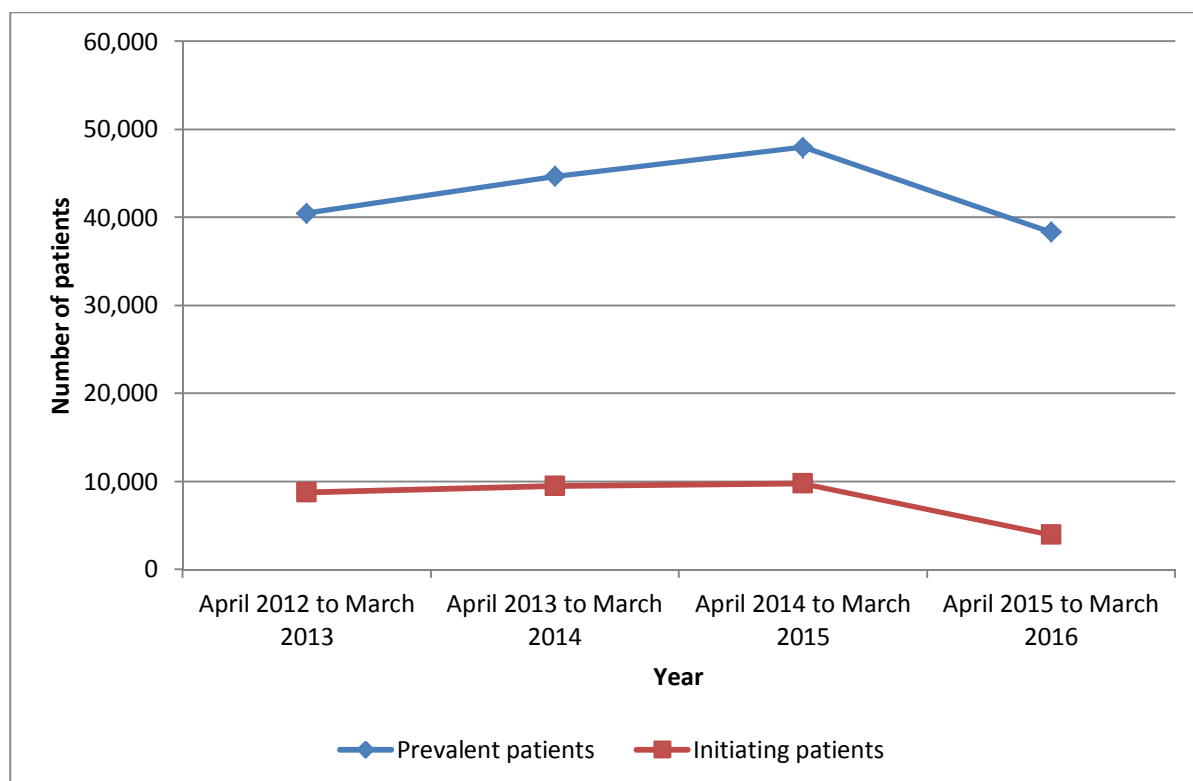


Figure 3: Number of patients initiating and prevalent to testosterone therapy in the years before and after the restriction change

Change to restriction occurred 1 April 2015. Source: DHS supplied prescription database accessed July 2016.

The number of initiating and prevalent patients in the year before and the year after the restriction change is presented in Table 5.

Table 5: Number of initiating and prevalent patients in the year before and after the restriction change with associated percentage change

| | April 2014 to March 2015 | April 2015 to March 2016 (% change) |
|---------------------|--------------------------|-------------------------------------|
| Initiating patients | 9,781 | 3,940 (-60%) |
| Prevalent patients | 47,995 | 38,364 (-20%) |

Change to restriction occurred 1 April 2015.

Source: DHS supplied prescription database accessed July 2016.

The number of patients supplied an initial prescription for testosterone increased by 12% over the three years from 1 April 2012 to 31 March 15. The number of initiating patients

was 60% lower in the year after the restriction change compared to the year before. The number of prevalent patients was 20% lower in the year after the change compared to the year before.

Patients initiating therapy by restriction

Figure 4 shows the number of initiating patients in the years surrounding the change by the restriction assigned to their first testosterone prescription.

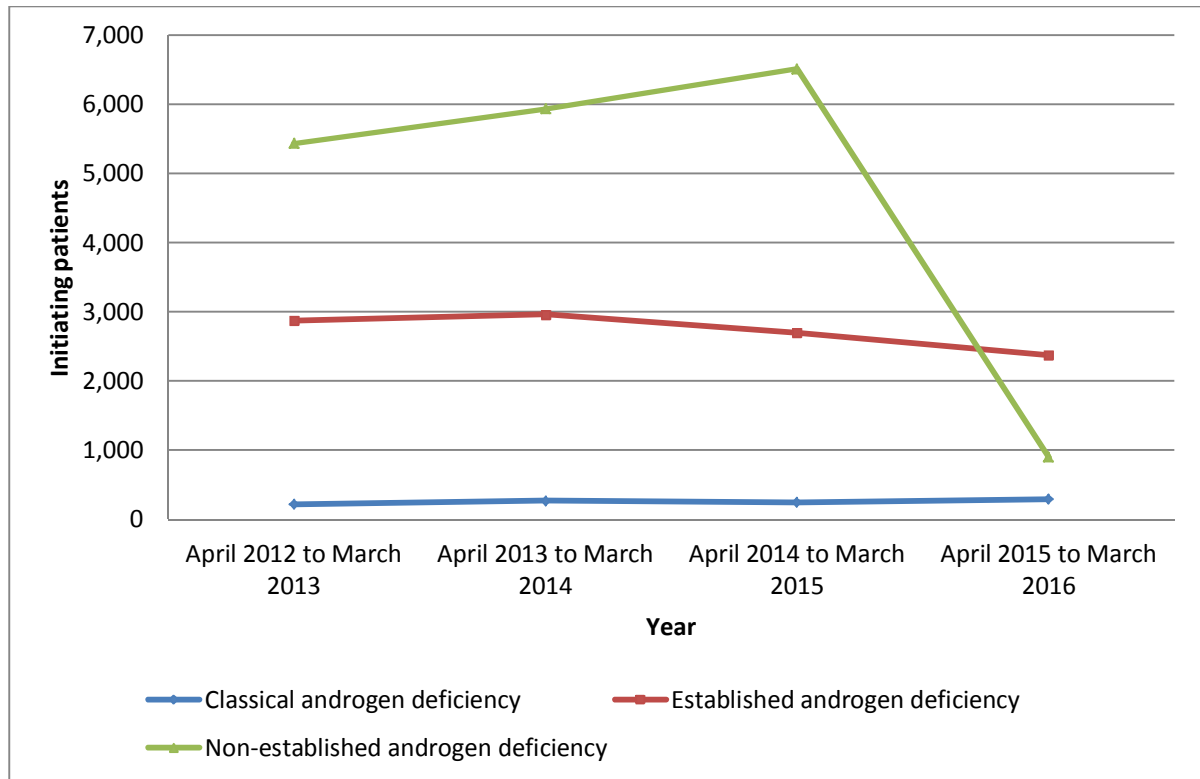


Figure 4: Initiating patients by all restrictions in the years surrounding the restriction change

Change to restriction occurred 1 April 2015. Classical androgen deficiencies defined as delay of growth/puberty, micropenis or pubertal induction. From April 2012 to March 2016, there were 1,220 initiating patients with an unknown or invalid restriction (not shown). Source: DHS supplied prescription database accessed July 2016.

There was a drop in initiating patients with non-established androgen deficiency in the year after the restriction change (86%). In the same time period, the number of patients initiating testosterone treatment for classical androgen deficiency did not decline.

Figure 5 depicts the proportions of initiating patients with the restriction codes for just the classical androgen deficiencies.

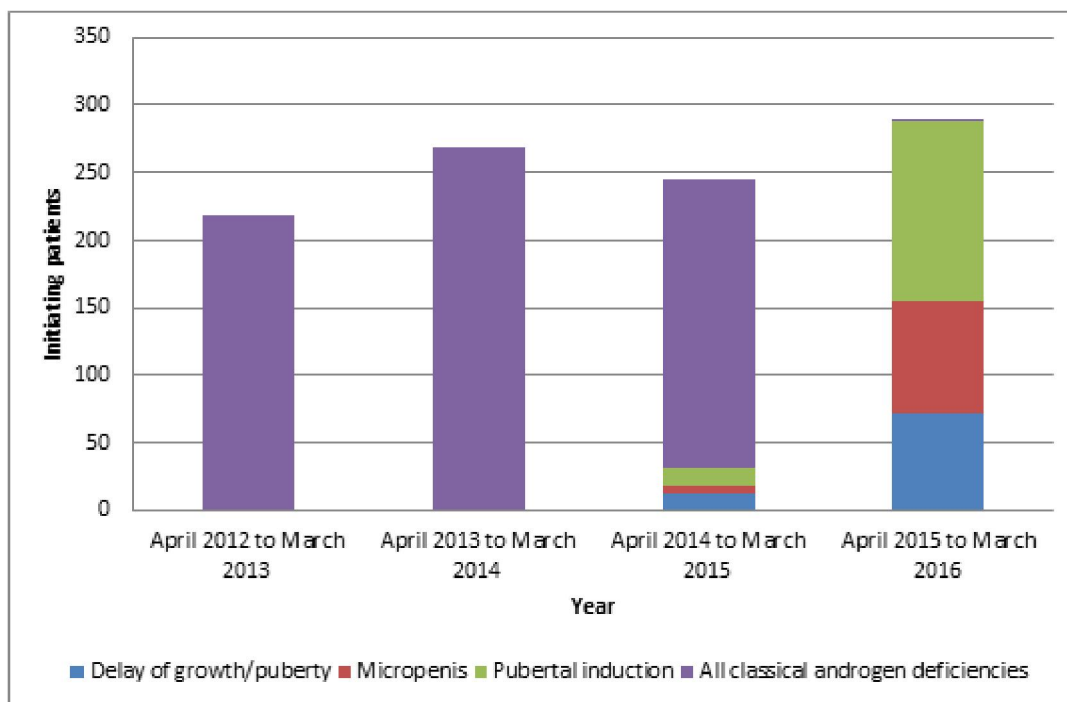


Figure 5: Initiating patients by classical androgen deficiency restrictions and year of supply

Change to restriction occurred 1 April 2015. Classical androgen deficiencies defined as delay of growth/puberty, micropenis or pubertal induction. From April 2012 to March 2016, there were 1,220 initiating patients with an unknown or invalid restriction (not shown). Source: DHS supplied prescription database accessed July 2016.

The individual restrictions for each of the classical androgen deficiencies came into effect on 1 March 2015. Prior to this, there was only one restriction that covered all three conditions, therefore prescribers did not need to specify a patient’s exact condition when obtaining the authority from DHS. In the year after the restriction change, there were two patients who were supplied a prescription with the non-specified classical androgen deficiency code. As the data is based on date of supply, these patients may have received a prescription with the code when it was still valid but had it dispensed after the code was no longer in effect.

Analysis by age

Figure 6 shows the age distribution of patients at their first testosterone supply in the years before and after the restriction change.

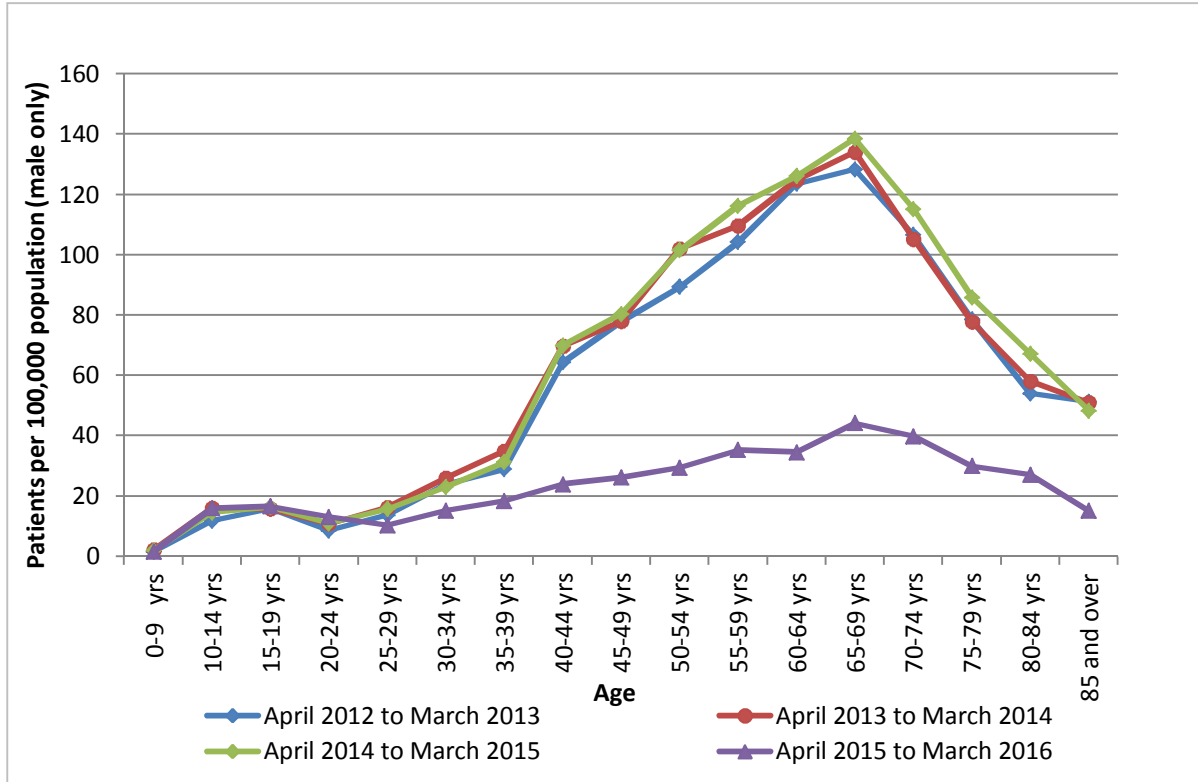


Figure 6: Patient age (standardised per 100,000 males) at initiation to testosterone therapy in the years before and after the restriction change

Change to restriction occurred 1 April 2015. Source: DHS supplied prescription database and ABS Quarterly Population Estimates (ERP), by State/Territory, Sex and Age database; accessed July and August 2016.

The age distribution of initiating patients was similar in the three years prior to the change in restriction. In all years, the peak use is at the same age bracket (65-69 years). For age brackets 40 years and over, there was a decline in the rate of people starting subsidised testosterone therapy of 60-73% in the year after the restriction change compared to the year before. The greatest percentage decline was in the 60-64 year group.

In the year after the change, there was little change in the rate of people commencing testosterone in the younger age groups.

Analysis by prescriber type

Figure 7 shows the number of patients supplied their first testosterone prescription by prescriber type in each year surrounding the restriction change on 1 April 2015.

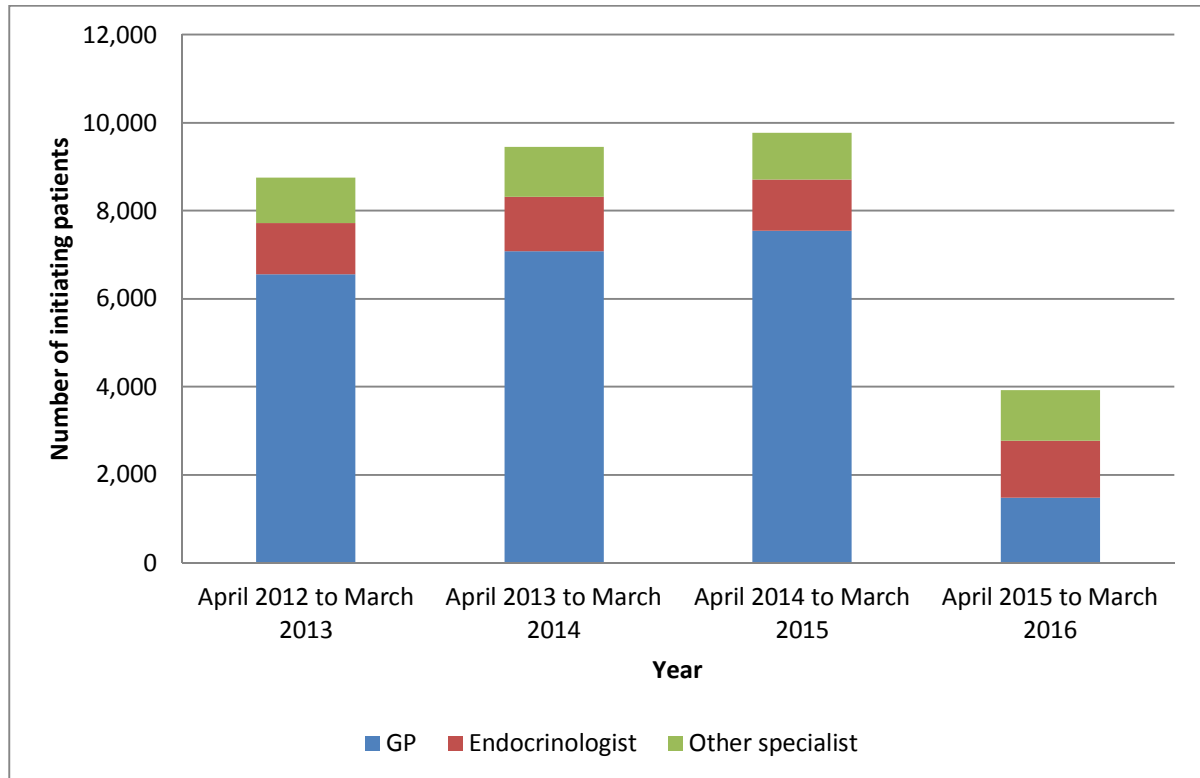


Figure 7: Patients supplied their first testosterone prescription by prescriber type and year

Change to restriction occurred 1 April 2015. Prescriber fields that were blank or unknown have been excluded (n=26). Source: DHS supplied prescription database accessed July 2016.

In the year after the restriction change (April 2015 to March 2016), the number of patients who had their initial testosterone prescription written by a GP was 80% lower than the previous year. In the year before the change, GPs prescribed 77% of the total initiating prescriptions compared to 38% in the year after the change. GPs can write a PBS prescription in consultation with a specialist or in the intervening period while patients wait for an appointment to be assessed by a specialist, but the patient still needs to qualify according to the androgen deficiency definition in the restriction.

The number of patients initiated to testosterone by endocrinologists and other specialists was similar in the years before the restriction change and the year after.

Original prescriptions analysis

To assess whether a higher proportion of patients discontinued testosterone after the change in the restriction an analysis of original prescriptions was conducted. Original PBS prescriptions usually provide a sufficient quantity and repeats for 6 months treatment, and

scripts remain valid for 12 months. Therefore it is expected that patients continuing on treatment would have at least one original prescription in a year.

Of the 86,605 patients supplied an original testosterone prescription between April 2013 and March 2014, 15% did not receive an original supply in the following 12 months (April 2014 to March 2015). Of the 92,729 patients supplied an original testosterone prescription the year before the restriction change, 38% were not supplied a subsequent original testosterone prescription in the year after the restriction change, indicating a higher rate of discontinuation.

Authority prescriptions

There was a change in the proportion of Authority prescriptions that were approved or rejected by the Department of Human Services before and after the restriction change. In the three months prior to April 2015, less than 5% of Authority prescriptions were rejected each month. In April, approximately one third were rejected. This decreased to approximately 25% rejected in May, down to 15% in August and fewer than 10% in December 2015 (DHS personal communication).

Private prescriptions

There was a shift in the proportion of private to PBS-subsidised testosterone prescriptions written in the year after the restriction change, according to MedicineInsight data. Prior to 1 April 2015, an average of 21% of prescriptions was private. This number increased to an average of 43% after the change.

Discussion

After the restriction change to R/PBS-subsidised testosterone for androgen deficiency that occurred on 1 April 2015, there was a decrease in the number of prescriptions supplied (Figure 1). The supply of all individual testosterone items declined after the restriction change (Figure 2). The intramuscular testosterone undecanoate injection and the transdermal gel were the two most commonly supplied testosterone items from October 2014 to March 2016.

The drop in the number of patients supplied R/PBS-subsidised testosterone therapy after the restriction change was driven more by a reduced number of new patients starting therapy than by existing patients stopping therapy (Figure 3 and Table 5). This may have been due to fewer patients meeting the new PBS restriction criteria. Further, fewer patients received a subsequent original prescription in the year after the restriction change, which indicates some existing patients ceased R/PBS-subsidised therapy. The reasons for patients not receiving subsequent original prescriptions cannot be determined and may not be due to the restriction change. The fewer patients initiating and the increase in patients stopping R/PBS-subsidised testosterone therapy may have been due to these patients

being supplied testosterone on private prescriptions. Prescribers may have also chosen alternative treatment pathways for patients, such as lifestyle changes.

The decrease in new patients was attributable to fewer older patients starting R/PBS-subsidised testosterone therapy. There was a large decrease in the number of patients over the age of 40 years who were supplied their first testosterone item in the year after the restriction change compared to the year before (Figure 6). The higher use in the older age groups in the years prior to the restriction change was noted by the PBAC at the August 2013 meeting.⁶ Concerns were raised at the time over potentially unnecessary use in older patients where clinical evidence and safety data are varied. The recent Endocrine Society of Australia position statement discusses testosterone treatment in older men.⁷ While healthy older men have lower testosterone concentrations on average than healthy, reproductively normal younger men,^{8,9} the long-term risks and benefits of testosterone treatment in these patients are unknown because large-scale, adequately powered and designed randomised controlled studies have not been performed.^{7,10}

Due to the range of factors that can contribute to androgen deficiency, GPs are often the first point of contact for symptomatic patients. Under the new testosterone restriction, patients must have been seen by or have an appointment booked with a specialist to be eligible for R/PBS-subsidised testosterone. Figure 7 shows that the number of initiations by GPs in the year after the change was far lower than in the three years before. This suggests that the change in restrictions had an impact on GP prescribing. The number of initiations by endocrinologists and other specialists did not differ greatly over the years of the analysis.

DUSC Consideration

DUSC discussed the issue raised by one of the sponsors that there may be people who have a therapeutic need for testosterone therapy who no longer qualify for PBS-subsidised supply. DUSC considered analyses provided by MedicineInsight showing that in the three months following 1 April 2015, the ratio of R/PBS to private prescriptions changed from 79%:21% in the previous quarter to 58%:42%. This suggests that there has been a shift to the private market. Overall, DUSC noted that, considering both the PBS/RPBS and private markets, the net result of the change in restriction was a reduction in the number of patients supplied testosterone.

⁶ Pharmaceutical Benefits Advisory Committee Public Summary Document 2013. Available at: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-08/testosterone>

⁷ Yeap et al. Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy. *Med J Aust* 2016; 205(4): 173-179. DOI: 10.5694/mja16.00393.

⁸ Piszczek J et al. The impact of drug reimbursement policy on rates of testosterone replacement therapy among older men. *PLoS One* 2014; 9(7): e98003. DOI: 10.1371/journal.pone.0098003.

⁹ Wang et al. Investigation, treatment and monitoring of late-onset hypogonadism in males. *Eu J Endocrinol* 2008; 159(5): 507-514.

¹⁰ Grossmann M. How to Treat: Low testosterone. *Australian Doctor* 26 June 2015; 23-30. Available at: www.australiandoctor.com.au Accessed 11 July 2016.

There was a large decrease in the number of patients over the age of 40 years who were supplied their first testosterone item in the year after the restriction change compared to the year before. DUSC noted that this effect was consistent with the more extensive restriction changes being for patients 40 years or older.

DUSC noted the T4DM trial² and that there might be a number of patients recruited into the trial who would have otherwise received PBS-subsidised testosterone. DUSC also noted that the outcomes of the trial might be informative with regards to using testosterone in overweight men.

DUSC noted that the sponsor response and a number of clinical groups raised concerns regarding potential issues with accessing specialist prescribers, particularly in regional and remote areas. Under the revised testosterone restriction, patients must have been seen by, be in consultation with, or have an appointment booked with a specialist to be eligible for R/PBS-subsidised testosterone. DUSC noted that specialist prescribing has remained fairly constant but that GP prescribing has declined. The higher levels of GP prescribing before 1 April 2015 may have been due to a number of factors such as sponsor promotion of new products. DUSC noted some clinical groups' comments that the wording of the restriction with regards to specialist consultation was too restrictive. Some responses suggested that an auditing process for patient attendance to specialist appointments should be in place. DUSC considered that the restriction wording, which permits prescribing 'in consultation with' one of the listed specialists, addresses the access concerns and that no further action is required.

In their response, one clinical group requested a change in the restriction for patients under 18 years old to remove the requirement for specialist involvement or to include general paediatricians in the list of specialists. DUSC referred this request to the PBAC for consideration.

A number of groups responded to the report debating the evidence of testosterone use in adult patients with and without established androgen deficiency. These concerns related to various clinical criteria in the restriction. DUSC noted the concerns raised and acknowledged that there are various and conflicting views surrounding appropriate testosterone therapy. There were several groups that suggested rewording of the current restriction regarding prescribers, gender and accessibility. Whilst DUSC acknowledged that there are many perspectives, DUSC did not consider there was a strong case to refer these suggested restriction wording changes to the PBAC. DUSC suggested that the effects of the restriction change to remove the word 'male' that occurred 1 October 2015 be monitored and considered for review at a later date.

DUSC Actions

DUSC requested that the report, stakeholder responses, MedicineInsight report and DUSC minutes 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

Various sponsors: no comments received.

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 Subcommittee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication. To the extent provided by law, DoH makes no warranties or representations as to accuracy or completeness of information contained in this report. To the fullest extent permitted by law, neither the DoH nor any DoH employee is liable for any liability, loss, claim, damage, expense, injury or personal injury (including death), whether direct or indirect (including consequential loss and loss of profits) and however incurred (including in tort), caused or contributed to by any person's use or misuse of the information available from this report or contained on any third party website referred to in this report.

Appendix A

Table A.1: R/PBS restriction codes for classical androgen deficiencies

| Restriction code | Restriction | Date onto PBS | Date off PBS |
|------------------|---|---------------|------------------|
| 1226 | Micropenis, pubertal induction, or constitutional delay of growth or puberty, in males under 18 years of age | 1 May 2000 | 28 February 2015 |
| 4816 | Constitutional delay of growth or puberty Population criteria: * Patient must be male, AND * Patient must be under 18 years of age. | 1 March 2015 | 31 March 2015 |
| 4818 | Micropenis Population criteria: * Patient must be male, AND * Patient must be under 18 years of age. | | |
| 4819 | Pubertal induction Population criteria: * Patient must be male, AND * Patient must be under 18 years of age. | | |
| 4867 | Micropenis Population criteria: * Patient must be male, AND * Patient must be under 18 years of age. Treatment criteria: * Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists. The name of the specialist must be included in the authority application. | 1 April 2015 | 31 July 2015 |
| 4869 | Pubertal induction Population criteria: * Patient must be male, AND * Patient must be under 18 years of age. Treatment criteria: * Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists. The name of the specialist must be included in the authority application. | | |
| 4870 | Constitutional delay of growth or puberty Population criteria: * Patient must be male, AND * Patient must be under 18 years of age. Treatment criteria: * Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine; or in consultation | | |

| Restriction code | Restriction | Date onto PBS | Date off PBS |
|------------------|---|----------------|--------------|
| | with one of these specialists; or have an appointment to be assessed by one of these specialists. The name of the specialist must be included in the authority application. | | |
| 5449 | Micropenis Population criteria: * Patient must be under 18 years of age. Treatment criteria: * Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists. The name of the specialist must be included in the authority application. | 1 October 2015 | - |
| 5460 | Pubertal induction Population criteria: * Patient must be under 18 years of age. Treatment criteria: * Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists. The name of the specialist must be included in the authority application. | | |
| 5471 | Constitutional delay of growth or puberty Population criteria: * Patient must be under 18 years of age. Treatment criteria: * Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists. The name of the specialist must be included in the authority application. | | |

Appendix B

Table B.1: Changes to R/PBS testosterone restriction text for androgen deficiency with established pituitary or testicular disorders

| Restriction number | Summary of change | Restriction Text | Start date | End date |
|--------------------|--|---|----------------|-------------------|
| 1022 | N/A | Androgen deficiency in males with established pituitary or testicular disorders | 1 May 2000 | 28 February 2015 |
| 4817 | Re-formatted | Androgen deficiency Clinical criteria: * Patient must have an established pituitary or testicular disorder. Population criteria: * Patient must be male. | 1 March 2015 | 31 March 2015 |
| 4868 | Added involvement of a specialist and requirement to provide specialist's details. | Androgen deficiency Clinical criteria: * Patient must have an established pituitary or testicular disorder. Population criteria: * Patient must be male. Treatment criteria: * Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists. The name of the specialist must be included in the authority application. | 1 April 2015 | 30 September 2015 |
| 5511 | Removed 'patient must be male' | Androgen deficiency Clinical criteria: * Patient must have an established pituitary or testicular disorder. Treatment criteria: * Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists. The name of the specialist must be included in the authority application. | 1 October 2015 | - |

Table B.2: Changes to R/PBS testosterone restriction text for androgen deficiency without established pituitary or testicular disorders

| Restriction number | Summary of change | Restriction Text | Start date | End date |
|--------------------|---|---|--------------|-------------------|
| 1021 | N/A | Androgen deficiency in males 40 years and older who do not have established pituitary or testicular disorders other than aging, confirmed by at least 2 morning blood samples taken on different mornings. Androgen deficiency is confirmed by testosterone less than 8 nmol per L, or 8-15 nmol per L with high LH (greater than 1.5 times the upper limit of the eugonadal reference range for young men) | 1 May 2000 | 28 February 2015 |
| 4815 | Re-formatted | <p>Androgen deficiency</p> <p>Clinical criteria:</p> <ul style="list-style-type: none"> * Patient must not have established pituitary or testicular disorders other than ageing. <p>Population criteria:</p> <ul style="list-style-type: none"> * Patient must be male, AND * Patient must be aged 40 years or older. <p>Androgen deficiency is defined as:</p> <ul style="list-style-type: none"> (i) testosterone level of less than 8 nmol per litre; OR (ii) testosterone level between 8 and 15 nmol per litre with high luteinising hormone (LH) (greater than 1.5 times the upper limit of the eugonadal reference range for young men) <p>Androgen deficiency must be confirmed by at least two morning blood samples taken on different mornings.</p> | 1 March 2015 | 31 March 2015 |
| 4866 | Added that the condition must not be due to age, obesity, cardiovascular diseases, infertility or | <p>Androgen deficiency</p> <p>Clinical criteria:</p> <ul style="list-style-type: none"> * Patient must not have an established pituitary or testicular disorder, AND * The condition must not be due to age, obesity, cardiovascular diseases, infertility or drugs. <p>Population criteria:</p> <ul style="list-style-type: none"> * Patient must be male, AND * Patient must be aged 40 years or older. <p>Treatment criteria:</p> | 1 April 2015 | 30 September 2015 |

| Restriction number | Summary of change | Restriction Text | Start date | End date |
|--------------------|--|---|----------------|----------|
| | <p>drugs.</p> <p>Added involvement of a specialist.</p> <p>Changed the qualifying testosterone and LH levels.</p> <p>Added requirement for test results and specialist details to be provided.</p> | <p>* Must be treated by a specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.</p> <p>Androgen deficiency is defined as:</p> <ul style="list-style-type: none"> (i) testosterone level of less than 6 nmol per litre; OR (ii) testosterone level between 6 and 15 nmol per litre with high luteinising hormone (LH) (greater than 1.5 times the upper limit of the eugonadal reference range for young men, or greater than 14 IU per litre, whichever is higher). <p>Androgen deficiency must be confirmed by at least two morning blood samples taken on different mornings. The dates and levels of the qualifying testosterone and LH measurements must be, or must have been provided in the authority application when treatment with this drug is or was initiated. The name of the specialist must be included in the authority application.</p> | | |
| 5474 | Removed 'patient must be male' | <p>Androgen deficiency</p> <p>Clinical criteria:</p> <ul style="list-style-type: none"> * Patient must not have an established pituitary or testicular disorder, AND * The condition must not be due to age, obesity, cardiovascular diseases, infertility or drugs. Population criteria: * Patient must be aged 40 years or older. <p>Treatment criteria:</p> <ul style="list-style-type: none"> * Must be treated by a specialist urologist, specialist endocrinologist or a registered member of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists. <p>Androgen deficiency is defined as:</p> <ul style="list-style-type: none"> (i) testosterone level of less than 6 nmol per litre; OR | 1 October 2015 | - |

| Restriction number | Summary of change | Restriction Text | Start date | End date |
|--------------------|-------------------|--|------------|----------|
| | | <p>(ii) testosterone level between 6 and 15 nmol per litre with high luteinising hormone (LH) (greater than 1.5 times the upper limit of the eugonadal reference range for young men, or greater than 14 IU per litre, whichever is higher).</p> <p>Androgen deficiency must be confirmed by at least two morning blood samples taken on different mornings. The dates and levels of the qualifying testosterone and LH measurements must be, or must have been provided in the authority application when treatment with this drug is or was initiated. The name of the specialist must be included in the authority application.</p> | | |

Appendix C

Table C.1: Dosage and administration of testosterone products

| Brand name and sponsor | Product | Dose and frequency of administration |
|--|--|--|
| Primoteston® Bayer Australia Ltd | Testosterone enanthate intramuscular injection | For the development and stimulation of still underdeveloped androgen-dependent target organs and for the initial treatment of deficiency symptoms: 250 mg IM every 2-3 weeks. To maintain an adequate androgenic effect, 250 mg IM every 3-4 weeks. Shorter or longer injection intervals may be necessary depending on the individual requirement for hormone. Serum testosterone levels should be measured before start of treatment and periodically during the treatment as recommended by current treatment guidelines. |
| Reandron® Bayer Australia Ltd | Testosterone undecanoate intramuscular injection | 1 g every 10 to 14 weeks IM where testosterone deficiency has been confirmed by clinical features and biochemical tests. |
| Andriol Testocaps® Merck Sharp & Dohme Pty Ltd | Testosterone undecanoate oral capsules | The initial dose is usually 120-160 mg/day for 2-3 weeks. Subsequent dosage (40-120 mg/day) should be based on the clinical effect obtained in the first weeks of therapy. Must be taken orally with the morning and evening meal. If an uneven number of capsules are to be taken, the greater dose should be taken in the morning. |
| Testogel® Besins Healthcare Australia Pty Ltd | Testosterone topical gel in sachets | 5 g of gel (i.e. 50 mg of testosterone which equates to four pump actuations, two 25 mg sachets or one 50 mg sachet) applied once daily at about the same time, preferably in the morning. The daily dose should be adjusted by the doctor depending on the clinical or laboratory response in individual patients, not exceeding 10 g of gel per day. The adjustment of dosage should be achieved by 2.5 g of gel steps. |
| Testogel® Besins Healthcare Australia Pty Ltd | Testosterone topical gel in pump pack | Each pump actuation delivers 12.5 mg of testosterone in 1.25 g of gel and to obtain the equivalent of 50mg of testosterone, 4 pump actuations are needed. Dose titration as above. |
| Axiron® Eli Lilly Australia Pty Ltd | Testosterone topical liquid for axillary application | 60mg of testosterone (3 mL or one pump actuation of 30mg testosterone applied to each underarm) once daily at approximately the same time each day. |

| Brand name and sponsor | Product | Dose and frequency of administration |
|--|--|--|
| Androforte® Lawley Pharmaceuticals Pty Ltd | Testosterone cream | The recommended dose is 2 mL of cream (i.e. 100 mg of testosterone) applied once daily at about the same time, preferably in the morning. The daily dose should be adjusted by the doctor depending on the clinical or laboratory response in individual patients, not exceeding 4 mL of cream per day. The adjustment of dosage should be achieved by 1 mL of cream steps. |
| Androderm® Allergan Australia Pty Ltd | Testosterone transdermal patch | 5 mg/day transdermal patch applied nightly (approximately 10.00pm) and worn for 24 hours, providing approximately 5 mg testosterone per day. The dose can be adjusted up to 7.5 mg/day (i.e., one 5 mg/day and one 2.5 mg/day patches or three 2.5 mg/day patches) nightly or down to 2.5 mg/day (i.e., one 2.5 mg/day patch) nightly depending on the serum testosterone measured in the morning after the application. Measurement of serum testosterone should be repeated taking care to ensure proper patch adhesion and correct time of application before the dose is adjusted. Treatment in non-virilised patients may be initiated with one Androderm® 2.5 mg/day patch applied nightly. The dose should be adjusted as appropriate. Three patches per day may be required for men with a higher body weight (>130kg). The duration of treatment and frequency of testosterone measurements is determined by the physician. |
| Sustanon 250® Aspen Pharmacare | Testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, testosterone decanoate (testosterone esters) | In general, dosage should be adjusted according to the response of the individual patient. Adults including elderly: Usually, one injection of 1mL per three weeks is adequate for Sustanon '250'. Sustanon should be administered by deep intramuscular injection. |

Source: Product Information accessed on TGA website¹¹

¹¹ Available from <https://www.ebs.tga.gov.au> Accessed 6 July 2016.