

Febuxostat: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

September 2018

Abstract

Purpose

To compare the predicted and actual utilisation of febuxostat during the first 24 months of PBS listing (1 September 2015 to 1 August 2017).

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Febuxostat was listed on the PBS on 1 September 2015.

Data Source / methodology

Data for febuxostat was extracted from the Department of Human Services (DHS) prescription database from the date of listing on the PBS Schedule on 1 September 2015 to December 2017 (inclusive).

Key Findings

- The total number of patients supplied febuxostat was 2,421 in the first year and 4,881 in the second year of PBS listing. There were fewer patients than predicted in both years.
- The number of prescriptions supplied and Government expenditure were also lower than expected.

Purpose of analysis

To compare the predicted and actual utilisation of febuxostat during the first 24 months of PBS listing (1 September 2015 to 1 August 2017).

Background

Clinical situation

Gout is a form of inflammatory arthritis affecting 1.7% of Australians.¹ It is caused by the deposition of urate crystals in the body, in particular the joints, soft tissues and kidneys.^{1,2} Gout is characterised by a sudden onset of joint pain and swelling which may be an initial or recurrent acute attack, chronic gouty arthritis or an acute attack in patients with underlying chronic gouty arthritis.²

The risk of gout increases with high levels of uric acid in the bloodstream and low clearance of uric acid from the body. However, gout may also occur in patients with normal uric acid concentration.^{1,2}

The management of acute attacks involves treatment with non-steroidal anti-inflammatory drugs (NSAIDs), colchicine or corticosteroids.^{1,2}

After the management of an acute attack, urate-lowering therapy (ULT) is recommended to manage serum uric acid concentration and prevent the formation of urate crystals.^{1,2} Allopurinol is recommended in Australian guidelines as a first line ULT. In patients hypersensitive or intolerant to allopurinol, febuxostat or probenecid should be considered.² In patients with a poor response to allopurinol, only probenecid is recommended.²

Prophylaxis with colchicine or NSAIDs is recommended when starting ULT in patients at a high risk of gout flare.^{1,2}

Despite the availability of treatments to manage gout, patient outcomes are often unsatisfactory due to poor adherence.³ Reported adherence rates to ULT vary widely worldwide and have been found to be as low as 9.6%.^{4,5,6,7}

Pharmacology

Febuxostat is a xanthine oxidase inhibitor that reduces the formation of uric acid in the blood and prevents acute flare-ups caused by the accumulation of uric acid.⁸

Therapeutic Goods Administration (TGA) approved indications

Febuxostat is indicated for the treatment of chronic symptomatic hyperuricaemia in conditions where urate deposition has already occurred (gouty arthritis and/or tophus formation) in adults with gout.³

Dosage and administration

The recommended starting dose of febuxostat is 40 mg once daily (achieved by halving one 80 mg tablet). The maintenance dose ranges from 40 mg to 80 mg once daily in accordance with serum uric acid level results with a target of less than 357 µmol/L.²

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

PBS listing details (as at July 2018)

Table 1: PBS listing of febuxostat

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
10445R	Febuxostat 80mg tablet, 28	1	5	\$51.18	Adenuric

Source: the [PBS website](#)

Restriction

Authority Required

Chronic gout

Clinical criteria:

- The condition must be either chronic gouty arthritis or chronic tophaceous gout, AND
- Patient must have a medical contraindication to allopurinol; OR
- Patient must have a documented history of allopurinol hypersensitivity syndrome; OR
- Patient must have an intolerance to allopurinol necessitating permanent treatment discontinuation

The listing includes a note that there is a shared care model for prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan.

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

Date of listing on PBS

1 September 2015

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

Febuxostat was first considered at the March 2014 meeting, where it was not recommended for PBS listing due to insufficient evidence of superiority compared to allopurinol in the requested first line setting. The PBAC recognised that there was a clinical

need for a second line alternative agent to treat chronic gout for patients who are intolerant to allopurinol. For further details, refer to the [Public Summary Document](#) from the March 2014 PBAC meeting.

The sponsor's resubmission sought a second line listing for febuxostat. At the March 2015 meeting, the PBAC recommended the listing of febuxostat for patients with chronic gout who are contraindicated to, or intolerant of, allopurinol. The recommendation was made on the basis of a clinical need for an alternative to probenecid in this population, and on the basis that febuxostat is likely to represent a cost-effective treatment compared to probenecid as a targeted, second-line treatment. To reduce the risk of unexpected Commonwealth expenditure on febuxostat if used beyond the recommended listing, the PBAC recommended that a risk share agreement be implemented whereby financial expenditure beyond an agreed level would be rebated to the Commonwealth. The PBAC did not recommend the listing for the allopurinol insufficient patient population due to inadequate clinical evidence to establish efficacy and safety. To address concerns about the use of febuxostat in the first line setting, the PBAC recommended an Authority Required listing and not an Authority Required (Streamlined) listing as requested by the sponsor. The PBAC recommended that DUSC review febuxostat usage two years after listing. For further details, refer to the [Public Summary Document](#) from the March 2015 PBAC meeting.

In July 2017, the sponsor submitted a request to amend the listing of febuxostat to Authority Required (Streamlined), claiming the number of prescriptions was lower than anticipated due to the Authority Required restriction being a prescribing barrier. While the utilisation was lower than anticipated, the PBAC was of the view that the current utilisation data could also suggest that the restriction is effectively targeting treatment to the right patient group. In addition, the use of febuxostat in allopurinol insufficient patients was not addressed in the submission. Therefore, the PBAC considered the previous concerns remained and that the Authority Required restriction remained appropriate to reduce the risk of prescribing outside of the current PBS restriction. The PBAC recommended that the utilisation and restriction level of febuxostat should be revisited after a DUSC review in twelve months' time. For further details, refer to the [Public Summary Document](#) from the July 2017 PBAC meeting.

Methods

PBS and RPBS prescription data for PBS-listed allopurinol, probenecid and febuxostat were extracted from the Department of Human Services (DHS) prescription database for the period April 2012 to June 2018 inclusive, based on the date that the prescription was supplied. Data for this period includes all R/PBS supplies regardless of whether a subsidy was paid; i.e. both over co-payment and under co-payment.

The R/PBS prescription data were used to determine the number of prescriptions supplied and R/PBS expenditure. These prescription data were also used to count the number of patients, both incident (new to pharmacological treatment) and prevalent (number treated) in each time period. The number of prevalent patients was determined by counting the number of people supplied at least one R/PBS prescription using

person-specific numbers (non-identifying) in the data for the specified time periods. Patient initiation date was defined as the date of supply of the first PBS or RPBS prescription of febuxostat. These prescription data were also used to determine the prescriber type for febuxostat prescriptions.

An analysis of scripts per patient in the 12 months after initiation of febuxostat on the PBS was also performed. This analysis was limited to patients that initiated from September 2015 to the end of August 2016, as this cohort of patients had at least 12 months of follow-up data after initiation.

A drug sequence analysis was undertaken for all previous ULT supplied in all patients initiating on febuxostat. Unique patient counts were derived for each sequence of treatment. The lookback period was to April 2012. Data prior to this are incomplete for general beneficiary patients as prescriptions for allopurinol priced under the general patient copayment were not captured.

A Kaplan Meier (aka Product-Limit) method was used to determine the length of treatment for patients on febuxostat. One analysis excluded any breaks in treatment and the other did not. A break in treatment was defined as a gap of more than three times the median time to resupply between supplies, which were an estimated break in treatment of at least two 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 if their last prescription was within three times the median time to resupply at this end date. Otherwise, the patient was deemed to have ceased treatment with the treatment coverage end date being the supply date of their last prescription plus a median time to resupply.

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

Results

Analysis of drug utilisation

Overall utilisation

The number of R/PBS prescriptions for febuxostat supplied per quarter since PBS listing is shown in Figure 1.

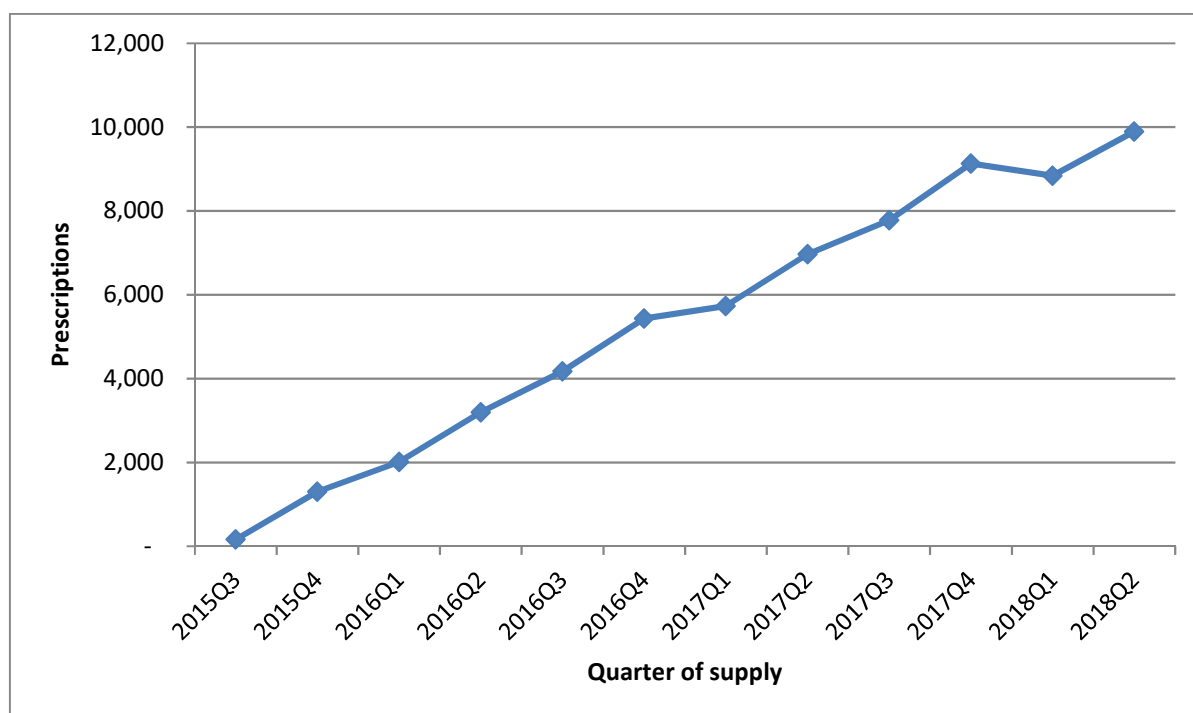


Figure 1: Number of R/PBS febuxostat prescriptions supplied per quarter

Source: DHS Prescriptions database, extracted August 2018

Figure 1 shows a continual increase in R/PBS febuxostat prescriptions supplied. The uptake of febuxostat has remained at a steady rate since listing in September 2015.

Patients initiating and prevalent to febuxostat therapy

Figure 2 shows the number of patients supplied febuxostat per quarter since R/PBS listing broken down into initiating and prevalent patients.

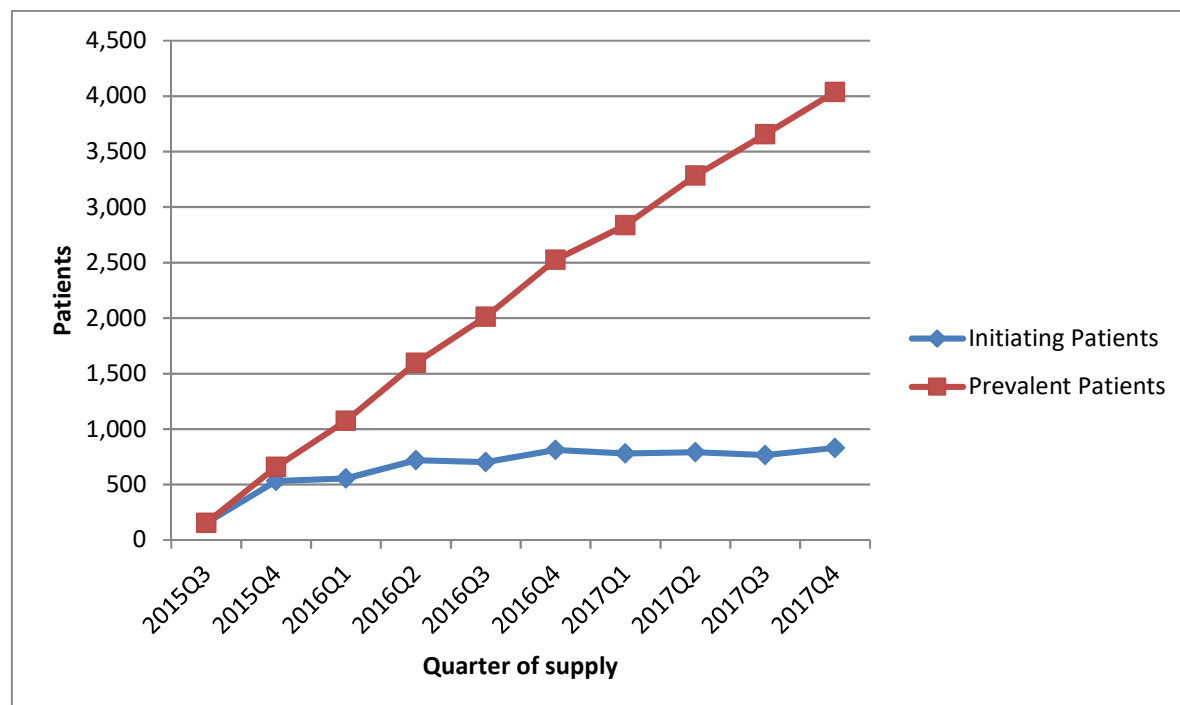


Figure 2: Number of initiating and prevalent patients to R/PBS febuxostat per quarter

Source: DHS Prescriptions database, extracted July 2018

The number of patients initiating febuxostat increased in each quarter of the first year of listing and plateaued in the second year of listing. The number of prevalent patients has retained a steady rate of growth since listing, likely due to the expectation that patients with chronic gout are to be managed lifelong on ULT.

Changes in the use of other drugs

The number of patients supplied allopurinol, febuxostat and probenecid is depicted in Figure 3. Figure 3a presents the same data for probenecid and febuxostat, zoomed in and presented as a stacked area, to show the extent to which patients supplied probenecid reduced with the listing of febuxostat. As probenecid and allopurinol have general PBS-listing statuses, the proportion of use for chronic gout cannot be differentiated from other indications such as allopurinol for tumour lysis syndrome and probenecid for the prolongation of penicillin serum levels. However, it is expected that the majority of use would be for chronic gout.

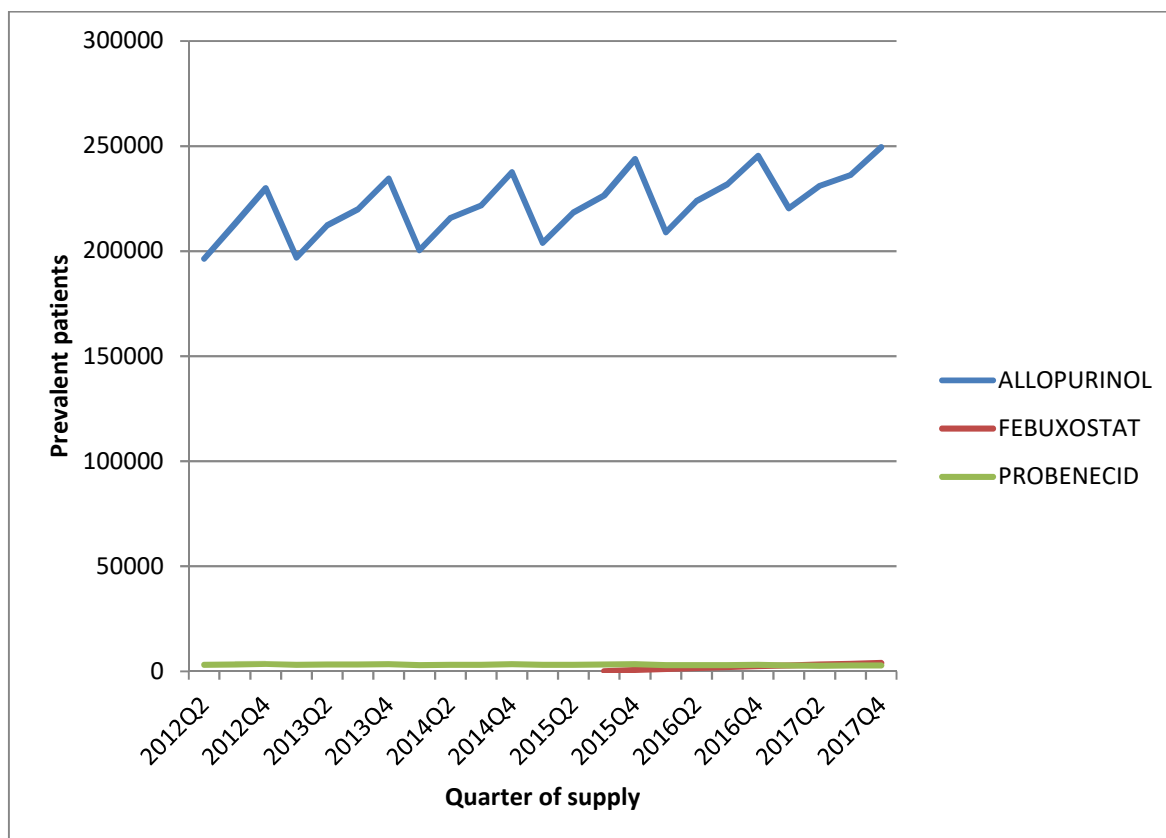


Figure 3: Number of prevalent patients by ULT medicine

Source: DHS Prescriptions database, extracted July 2018

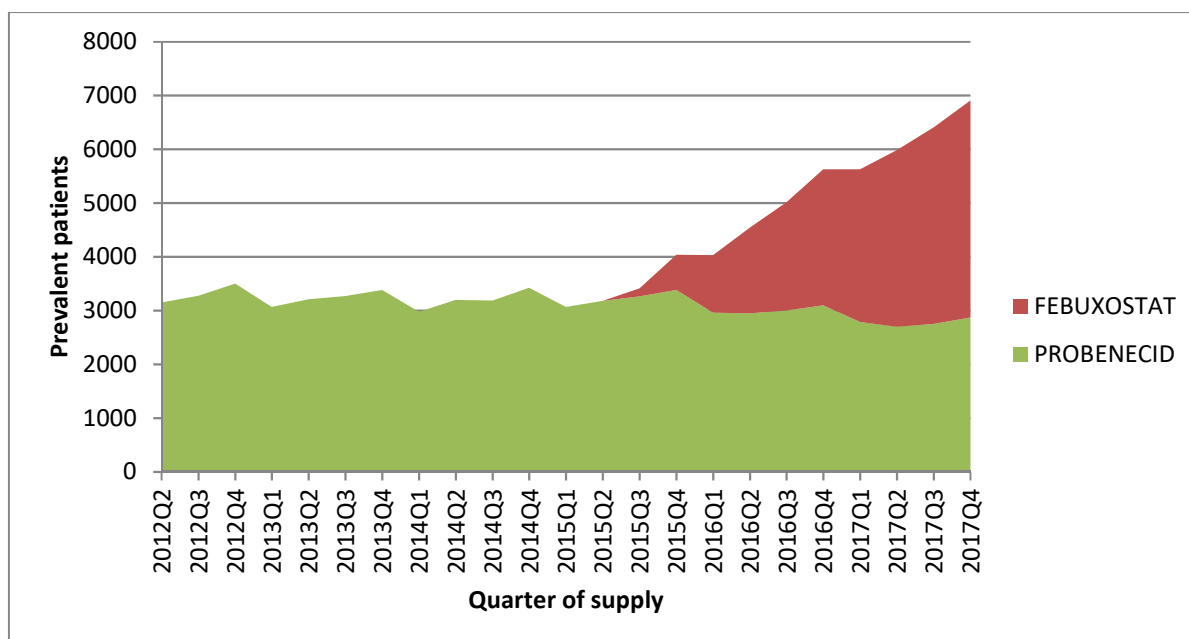


Figure 3a: Number of prevalent patients: probenecid and febuxostat

Source: DHS Prescriptions database, extracted July 2018

The number of patients supplied allopurinol did not seem to be affected by the listing of febuxostat (Figure 3). Since the listing of febuxostat, the number of patients supplied probenecid, which was previously stable, decreased; though not to the same extent as the uptake of febuxostat (Figure 3a).

Prior urate-lowering therapy

Figure 4 depicts patients initiating febuxostat per quarter by the proportion supplied previous ULT (since April 2012).

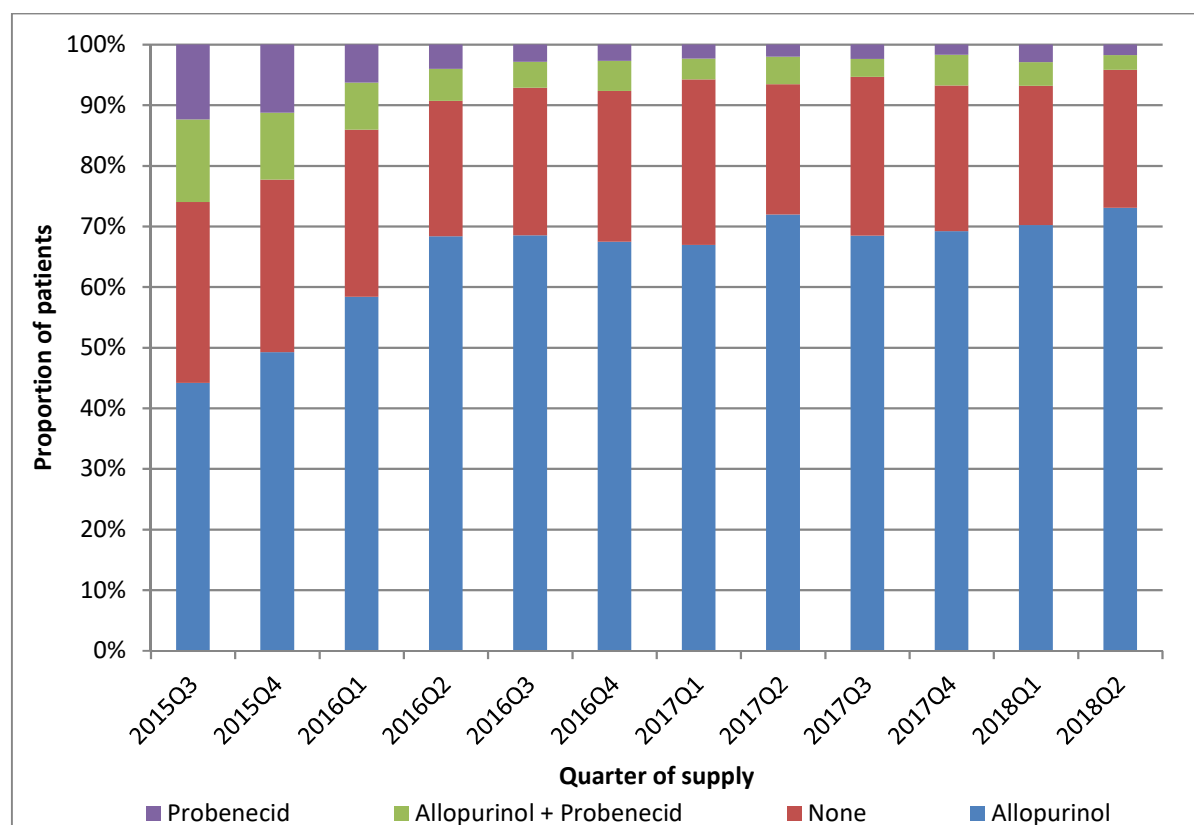


Figure 4: Proportion of patients supplied previous ULT prescriptions prior to initiation of febuxostat

Source: DHS prescriptions database, extracted July 2018

The majority of patients initiating febuxostat had previous supplies of allopurinol (67% on average). As the PBS listing of febuxostat is limited to allopurinol intolerant and contraindicated patients, the submission only anticipated a reduction in probenecid prescriptions from substitution. The proportion of febuxostat initiators who had previous supplies of probenecid reduced over time (26% in the first quarter of listing to 4% in quarter 2 2018; 9% average over the period). On average, 1 in 4 patients initiating febuxostat had not been supplied R/PBS subsidised allopurinol or probenecid in the analysis period (since April 2012) and this proportion was stable over the period.

Prescriptions per Patient

The number of prescriptions per patient in the 12 months after initiation was calculated (Figure 5) for febuxostat patients that initiated from September 2015 to the end of August 2016 (n=2,421); to allow for 12 months of follow-up for each patient.

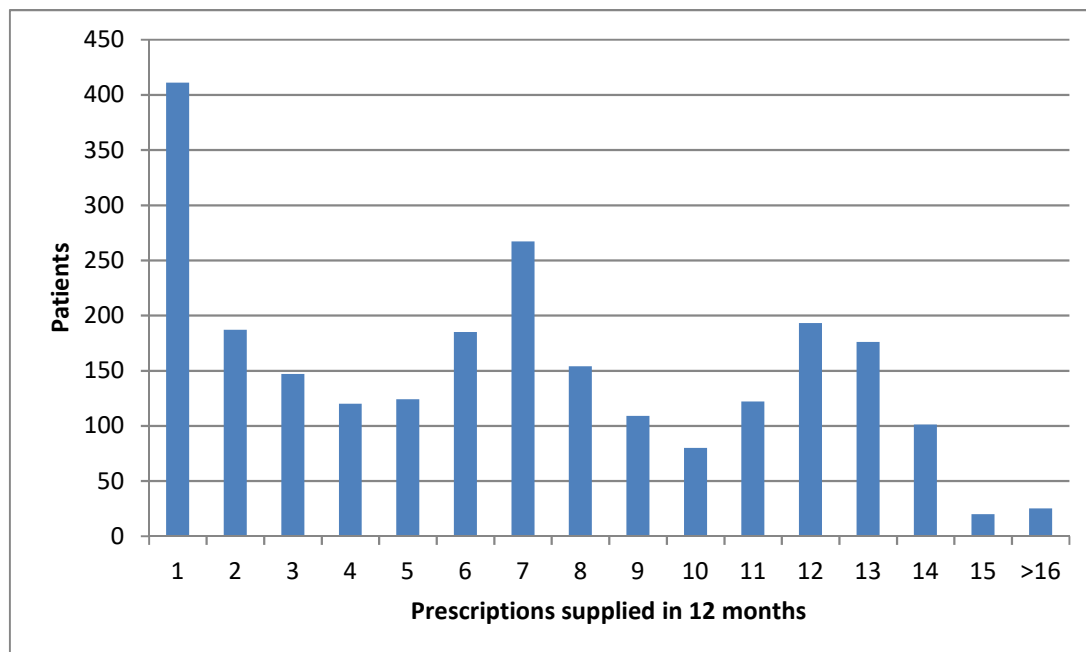


Figure 5: Distribution of the number of febuxostat prescriptions per patient 12 months post-initiation

Source: DHS prescriptions database, extracted July 2018

Out of the 2,421 patients, 17% received no further supplies of febuxostat in the 12 month period. A further 42.5% of patients had between two to seven supplies in the 12 month period. On average, patients received seven supplies per year in the first year of therapy; slightly fewer than predicted in the submission (██████). It is not possible from PBS data alone to determine the extent to which the lower number of prescriptions per patient is due to lower average dose than expected (70 mg/day) or poorer compliance (75%).

Prescriber type

The majority (78%) of supplied febuxostat prescriptions since PBS listing were prescribed by general practitioners. The febuxostat listing includes a shared care model for prescribing by nurse practitioners. However, since the time of febuxostat listing, there have been just 49 prescriptions supplied that were prescribed by a nurse practitioner. This 0.1% of the total number of prescriptions supplied (n=64,247).

Length of Time

Figure 6 depicts the Kaplan Meier estimates of length of treatment of febuxostat with and without breaks in treatment.

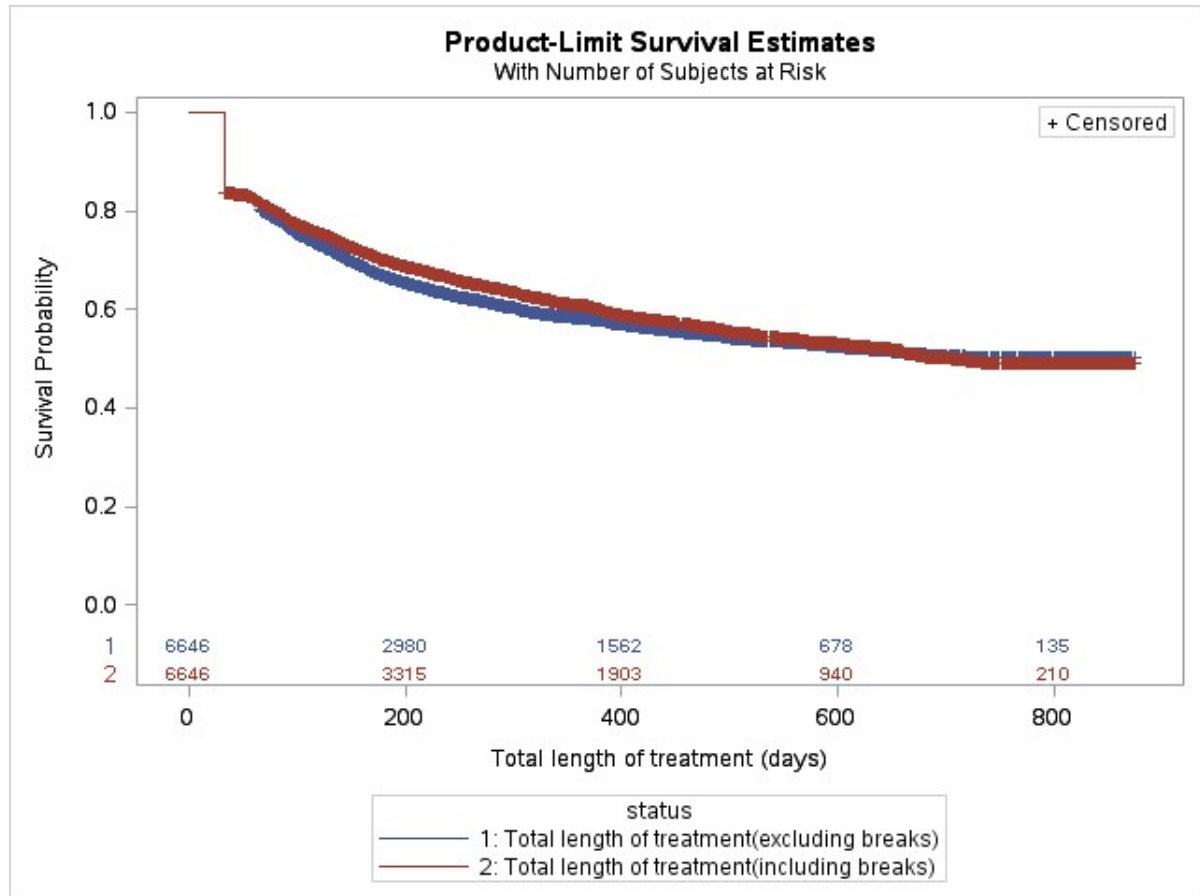


Figure 6: Length of treatment (days) with febuxostat

Source: DHS Prescriptions database, extracted July 2018

Approximately 15% of patients had no further prescriptions for febuxostat after the initial supply. Around 60% of patients remained on therapy after one year of therapy and around 50% of patients remained on therapy after two years.

The length of treatment is similar whether accounting for breaks or excluding breaks in therapy.

Analysis of actual versus predicted utilisation

A comparison of the estimated versus actual use of febuxostat for the first two years since listing is shown in Table 2.

Table 2: Analysis of actual versus predicted utilisation

		Year 1	Year 2
Patients	Predicted	██████	██████
	Actual	2,421	4,881
	% Difference	██████	██████
Prescriptions	Predicted	██████	██████
	Actual	9,352	24,755
	% Difference	██████	██████
Substituted probenecid prescriptions	Predicted	████	██████
	Actual#	651	1,421
	% Difference	██████	██████
Expenditure*	Predicted	██████████	██████████
	Actual	\$326,875	\$868,149
	% Difference	██████	██████

Source: [REDACTED], DHS prescriptions database (actual), extracted July 2018.

[#]Calculated as difference from previous year (September-August)

In both the first and second years of listing, the total number of patients that were supplied febuxostat was considerably less than the numbers predicted. This translated to a lower number of prescriptions and expenditure than expected.

Discussion

The utilisation of febuxostat continued to grow from the time of listing; as demonstrated by the increase in the total volume of prescriptions (Figure 1) and patients (Figure 2). However, the extent of uptake has not been as expected. In the first two years of listing, substantially fewer patients were supplied febuxostat than predicted (Table 2). The % difference in volume of prescriptions being lower than the % difference in the volume of patients may be due to fewer average prescriptions supplied per patient (actual of 7 compared to predicted 10, Figure 5).

The submission considered that patients supplied R/PBS febuxostat would include the probenecid-treated chronic gout population and the ULT-untreated chronic gout population. The analysis of previous ULT supplied showed that 9% of patients over the period had previously been supplied probenecid since April 2012 (Figure 4). The reduction in probenecid prescriptions with the listing of febuxostat (Table 2) was less than the predicted substitution in Year 1 but almost exactly as predicted in Year 2. This implies that,

although substitution for probenecid accounted for a small proportion of febuxostat use, it was close to predicted over the period. Therefore, although a quarter of patients supplied febuxostat had no previous ULT (since 2012), the lower than expected utilisation of febuxostat is largely due to less than expected uptake from the untreated population. The predicted uptake in the untreated population might have been optimistic if these patients weren't engaged with the health care system. Other possible explanations for lower than predicted use of febuxostat in this population include overestimation of:

- The number of eligible patients. The submission calculated the ULT population by applying a proportion of use in chronic gout (■■■■), average dose per day and compliance (■■■■) to the PBS prescriptions for allopurinol and probenecid. The submission's method provides a starting point for this population of over 200,000 patients in the index year (2012-2013 financial year), while PBS data shows the market at quarter 2 2013 was over 200,000 patients (Figure 3).
- The uptake rate. Febuxostat has been associated with an increase in risk of cardiovascular mortality.⁹ As patients with gout tend to have multiple co-morbidities (including cardiovascular diseases)², the use of febuxostat in this patient population may be limited in practice.

The length of treatment analysis (Figure 6) shows that less than 60% of patients remain on febuxostat after one year, consistent with the high rate of discontinuation (32%) in the febuxostat FOCUS study¹⁰ presented by the sponsor.

DUSC consideration

Febuxostat use, in terms of prescriptions and patients, continued to increase over the period. However, uptake has been lower than expected. In the first two years of listing, substantially fewer patients were supplied febuxostat than predicted. The percentage difference in volume of prescriptions being lower than the percentage difference in the volume of patients may be due to fewer average prescriptions supplied per patient (actual of 7 compared to predicted ■■■■). DUSC noted that a reason for there being fewer prescriptions per person cannot be determined from available data, but noted this may be due to lower doses or a lower rate of adherence than expected.

Although uptake from probenecid-treated patients was low, it was similar to predicted. Contrastingly, uptake in the untreated population was much lower than expected. DUSC noted that the lower than expected uptake from the untreated population was the main contributor to febuxostat use being lower than anticipated. DUSC considered that the eligible population may have been overestimated. DUSC considered that the uptake of febuxostat may also be tempered by concerns regarding cardiovascular safety. While the publication concerning cardiovascular safety¹ is recent (March 2018), concerns have been foreshadowed by the FDA for some time.

¹ White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, et al. Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout. N Engl J Med 2018; 378: 1200-1210. DOI: 10.1056/NEJMoa1710895

DUSC recalled that the PBAC considered an application from the sponsor in July 2017² which requested the authority level be changed from Authority Required (telephone) to Authority Required (STREAMLINED). The PBAC rejected the request as the restriction appeared to be appropriately targeting therapy, and there remained a risk of prescribing outside of the current PBS restriction, particularly in allopurinol insufficient patients, for whom there was a paucity of evidence of efficacy and safety. Considering the PBAC outcome, the utilisation data and the safety signals, DUSC considered it would be appropriate for the restriction to remain as Authority Required.

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

A.Menarini Australia: The Sponsor has no comment

² [July 2017 PBAC public summary document](#)

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