# bDMARDs for psoriatic arthritis: addendum to the October 2015 analysis

## Drug utilisation sub-committee (DUSC)

***February 2016***

## Abstract


***Purpose***

To assess the utilisation of disease modifying anti-rheumatic drugs (DMARD) prior to initiation of biological DMARDs (bDMARDs) for psoriatic arthritis.

***Date of listing on the Pharmaceutical Benefits Scheme (PBS) for this indication***

- Adalimumab: 1 August 2006
- Etanercept: 1 August 2006
- Infliximab: 1 August 2006
- Golimumab: 1 August 2010
- Certolizumab pegol: 1 April 2015

***Data Source / methodology***

The DHS prescription claims database was used for the analyses in this addendum.

***Key Findings***

- Approximately 17% of patients may not have trialled methotrexate and sulfasalazine or leflunomide prior to their first bDMARD in accordance with the PBS restriction. Patients with a contraindication are exempt from this requirement for the relevant medicine.
- The proportion of patients trialling none of the restriction specified drugs (methotrexate, sulfasalazine and leflunomide) may be slowly increasing (see Figure 1).
- At initiation to bDMARD therapy for psoriatic arthritis, 35% of patients added the bDMARD to an existing DMARD regimen, 52% of patients substituted one or more drugs in an existing DMARD regimen and 13% initiated without having been on any DMARD at the time.
- At initiation 40% of patients were on bDMARD monotherapy and 60% were using a combination of DMARD and bDMARD. Twelve months after initiation 42% of patients were on bDMARD monotherapy and 58% were using a combination of DMARD and bDMARD.

# Background

The DUSC considered a report on the use of bDMARDs at its October 2015 meeting. A public release version of this report is available[1]. At this meeting the DUSC requested that "*…an assessment of DMARD use prior to initiation on bDMARDs for psoriatic arthritis be undertaken and presented to DUSC at a future meeting…".*

To be eligible for a PBS subsidised bDMARD for psoriatic arthritis the patients must have:

failed to achieve an adequate response to methotrexate at a dose of at least 20 mg weekly for a minimum period of 3 months,

AND

failed to achieve an adequate response to sulfasalazine at a dose of at least 2 g per day for a minimum period of 3 months; OR

failed to achieve an adequate response to leflunomide at a dose of up to 20 mg daily for a minimum period of 3 months.

Where treatment with methotrexate, sulfasalazine or leflunomide is contraindicated according to the relevant TGA-approved Product Information, details must be provided at the time of application for the initial treatment authority approval.

Where intolerance to treatment with methotrexate, sulfasalazine or leflunomide developed during the relevant period of use, which was of a severity to necessitate permanent treatment withdrawal, details of the degree of this toxicity must be provided at the time of application.

# Methods

The analyses were undertaken using prescriptions supplied from August 2006 to September 2015 from the DHS prescription claims database. The first step was to find all the patients who had been supplied a bDMARD for psoriatic arthritis (PsA). Different cohorts of patients were used in each analysis as described further below.

The PBS item codes for bDMARDs are restriction specific. Item codes for PsA are shown in Table 1.

[1] http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/bdmard-psoriatic-arthritis-dusc-prd-2015-10-abstract

**Table 1: bDMARD PBS items for psoriatic arthritis**

| ATC code | Drug name | PBS item code | Form and strength |
|---|---|---|---|
| L04AB01 | Etanercept | 09035M | Injection set containing 4 vials powder for injection 25 mg and 4 pre-filled syringe |
| | | 09036N | Injection set containing 4 vials powder for injection 25 mg and 4 pre-filled syringe |
| | | 09087G | Injections 50 mg in 1 mL single use pre-filled syringes, 4 |
| | | 09088H | Injections 50 mg in 1 mL single use pre-filled syringes, 4 |
| | | 09457R | Injection 50 mg in 1 mL single use auto-injector, 4 |
| | | 09458T | Injection 50 mg in 1 mL single use auto-injector, 4 |
| L04AB02 | Infliximab | 05756Y | Powder for I.V. infusion 100 mg |
| | | 06496X | Powder for I.V. infusion 100 mg |
| L04AB04 | Adalimumab | 09033K | Injection 40 mg in 0.8 mL pre-filled syringe |
| | | 09034L | Injection 40 mg in 0.8 mL pre-filled syringe |
| | | 09101B | Injection 40 mg in 0.8 mL pre-filled pen |
| | | 09102C | Injection 40 mg in 0.8 mL pre-filled pen |
| L04AB05 | Certolizumab Pegol | 10238W | Injection 200 mg in 1 mL single use pre-filled syringe |
| L04AB06 | Golimumab | 03430M | Injection 50 mg in 0.5 mL single use pre-filled syringe |
| | | 03431N | Injection 50 mg in 0.5 mL single use pre-filled pen |
| | | 03432P | Injection 50 mg in 0.5 mL single use pre-filled syringe |
| | | 03433Q | Injection 50 mg in 0.5 mL single use pre-filled pen |

The next step was to extract all DMARDs for the PsA patients identified in step 1. The list of drugs to include in the DMARD category was determined from the Therapeutic Guidelines[2]. Due to data size considerations, the DMARD prescription supply time period was limited to January 2010 to September 2015. Table 2 shows the DMARDS that were extracted.

**Table 2: DMARDs extracted for all PsA patients**

| Drug Group | ATC code | Drug name |
|---|---|---|
| DMARDs | A07EC01 | Sulfasalazine |
| | L01BA01 | Methotrexate |
| | L01BB02 | Mercaptopurine |
| | L04AA13 | Leflunomide |
| | L04AD01 | Cyclosporin |
| | L04AX01 | Azathioprine |
| | M01CA | Hydroxychloroquine |

[2] eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; Accessed Nov 2015 <http://online.tg.org.au/complete/desktop/index.htm>.

***DMARDs supplied prior to initiation to bDMARD therapy for psoriatic arthritis***

Initiation was defined as the date of patient's first supply of a bDMARD since the listing of the first bDMARD for PsA in August 2006. The data extracted in step 2 enabled an analysis of prior DMARDs for all patients who initiated their first bDMARD therapy in the period January 2014 to September 2015 with a look back period of 4 years (i.e. to January 2010). The analysis was done with both a constant lookup period (i.e. each patient's DMARD prescription history started exactly 4 years prior to their bDMARD therapy initiation) and with at least 4 years look back (i.e. the DMARD history back to January 2010 was used for all patients, resulting in a 4 year look back period for patients initiating in January 2014 and a 5 year and 8 month look back period for patients initiating in September 2015). There was little difference between the two methods. The constant look back results are presented in this report as these avoid any bias in cohort comparison due to unequal look back periods.

***Estimated patient drug regimen analysis***

The analysis was undertaken for patients who initiated treatment with in the 12 month period October 2013 to September 2014 (inclusive). This cohort of patients was chosen because it is the most recent one that has a sufficient minimum follow-up period (i.e. 12 months to the end of September 2015).

This cohort had at least 3 years and 9 months pre-initiation prescription history. However only 18 months of the pre-initiation period is covered by the collection of under co-payment prescriptions (i.e. from April 2012).

For more details see Appendix A: Detailed methodology to estimate drug regimens and regimen transitions.

Data analysis was undertaken using SAS. As this analysis uses date of supply prescription data, there may be small differences compared with publicly available Department of Human Services (DHS) PBS date of processing data.[3]

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

## Results

### *DMARDs supplied prior to initiation to bDMARD therapy for psoriatic arthritis*

Figure 1 shows the percentage of patients that were supplied methotrexate and sulfasalazine or leflunomide anytime in the four years prior to the patient initiating bDMARD therapy for psoriatic arthritis, by quarter of initiation.

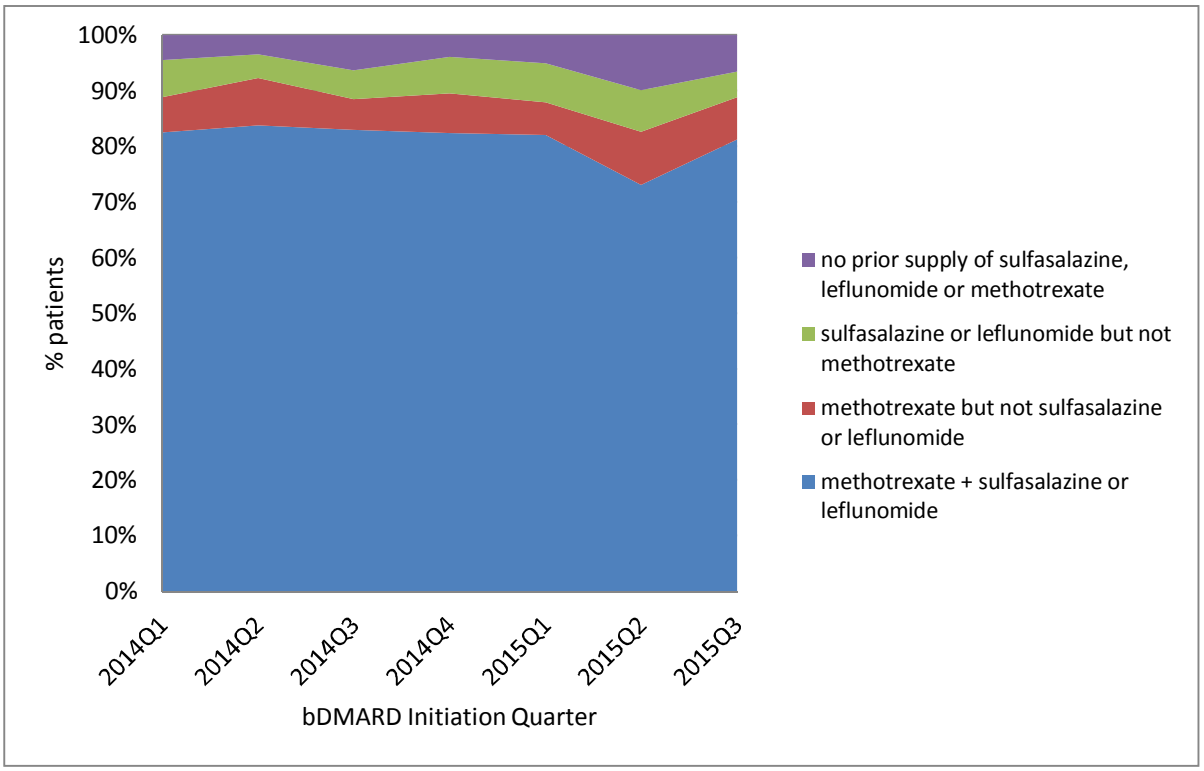


**Figure 1: Percent of patients supplied DMARDs of interest prior to initiating bDMARD therapy**

Note: Using prescription look back period of 4 years prior to bDMARD initiation for each patient.

In the third quarter of 2015 81.3% of patients (248 of 305 patients) had been supplied methotrexate and sulfasalazine or leflunomide in the 4 years prior to initiation to bDMARD therapy. This means that approximately 18.7% of patients that initiated in this quarter do not appear to have fulfilled the prior DMARD aspect of the restriction criteria. However, some of these patients may have a contraindication that exempts them from this requirement. The percentage of patients receiving no supply of any of the three drugs seems to be increasing slowly over time to 6.6% in 2015 Q3.

A sensitivity analysis was undertaken using a look back period of exactly 5 years from each patient's bDMARD initiation date (this was only possible for the three quarters in 2015). The result was 83.0% of patients had been supplied methotrexate and sulfasalazine or leflunomide prior to initiation in 2015 Q3 and so 17.0% of patients did not fulfil the prior

DMARD criteria. Thus the addition of an extra year of look back reduced the estimate of patients not fulfilling the prior DMARD criteria by 1.7%.

The reason for the different pattern of use in quarter 2 of 2015 is unknown.

The analysis in Figure 1 does not have regard to whether or not the restriction specified 3 months trial period or dose has been satisfied. As such the percentage of patients fulfilling the restriction criteria quoted above is a possible overestimate. That is, even if a patient has methotrexate and sulfasalazine or leflunomide prior to initiation they may still fail the duration and dose criteria.

Some strengths and pack sizes of methotrexate are priced under the general co-payment. As under co-payment data was not available in the PBS dataset prior to April 2012, the prescription history for methotrexate for general patients prior to this time will be missing. To address this limitation of the analysis, a sensitivity analysis was undertaken using a "concessional only" cohort, as these patients are more likely get methotrexate on the PBS for financial reasons (i.e. the concessional co-payment is less than PBS price and likely to be less than the private script price. Also PBS scripts contribute to a patient reaching the PBS Safety Net). Concessional only patients were defined as those who did not have any "General Patient" category prescriptions for DMARDs or bDMARDs in the 4 years prior to their initiation to bDMARD therapy. The results for these patients are shown in Figure 2.

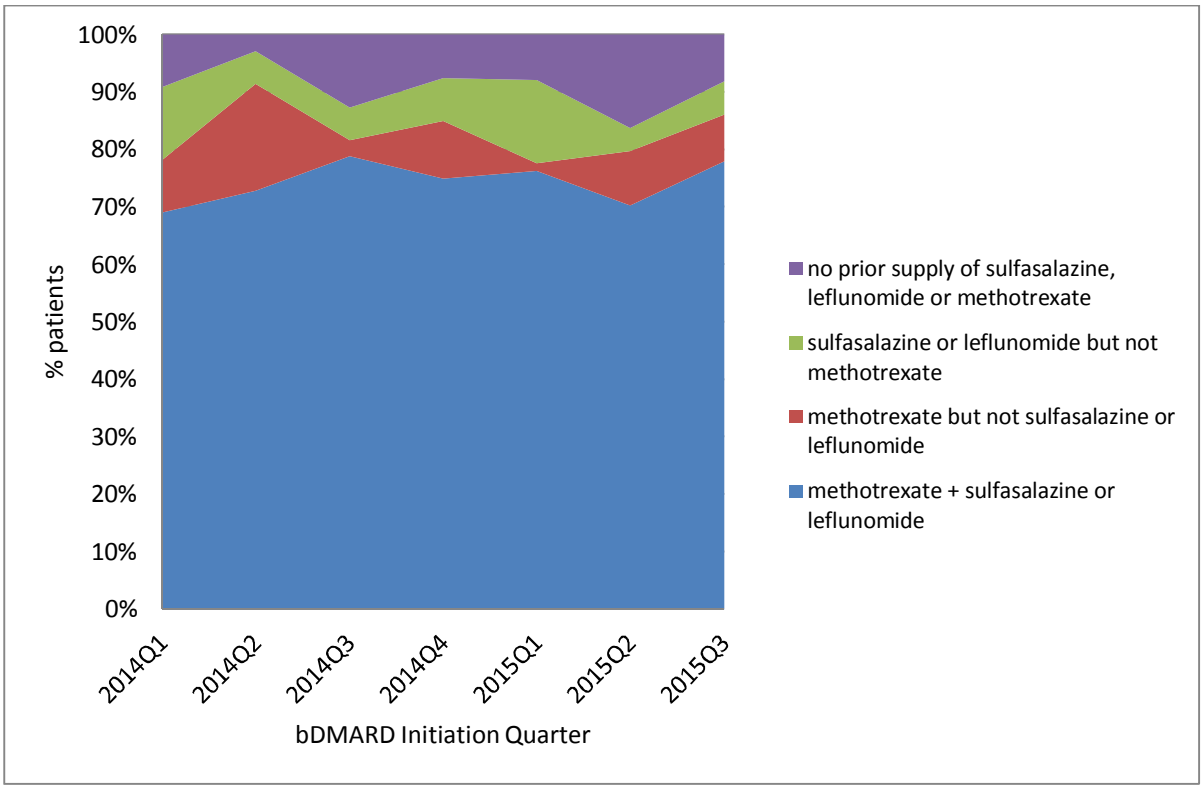


**Figure 2: Percent of concessional only patients by supply of DMARDs prior to initiation to**

**bDMARD therapy**

Note: Using prescription data back to 4 years prior to bDMARD initiation for each patient.

Comparison of Figure 2 with Figure 1 shows that the results for concessional only patients were similar to the analysis of the total PBS population for those categories that contain methotrexate. The percentage of patients who had been supplied methotrexate and at least one of sulfasalazine or leflunomide in the third quarter of 2015 was 81.3% for all patients (Figure 1) and 77.9% for concessional only patients (67 of 86 patients, Figure 2). Further, the percentage of patients who have received methotrexate but not sulfasalazine or leflunomide in the same period was 7.5% for all patients and 8.1% for concessional only patients. Overall, for the third quarter of 2015, 88.8% of all patients and 86.0% of concessional patients were supplied methotrexate, suggesting that the absence of under co-payment data prior to April 2012 has minimal impact on the findings of the analysis.

***Duration and Dose***

Testing compliance to the duration and dose intensity criteria in the PBS restriction could be undertaken by estimating the duration and average dose for the three drugs (methotrexate, sulfasalazine and leflunomide) for each patient. However this is complex task because the PBS data does not include information on the dose prescribed; doses can vary widely (both within a patient and across the population), and there are multiple pack sizes and strengths available.

As an alternative, some information about the duration of the drugs trialled can be inferred from the drug regimen analysis in the following section (see Figure 3).

### *Estimated Patient Drug Regimen transitions at initiation to bDMARD therapy*

The estimated patient drug regimen transitions at the point of initiation to bDMARD therapy for psoriatic arthritis are shown in the table below. These are for patients who initiated therapy in the 12 month period October 2013 to September 2014 (inclusive). See the Methods section for more details regarding this analysis and cohort.

**Table 3: Estimated drug regimen transitions at initiation to bDMARD therapy for psoriatic arthritis**

| Pre-initiation (week=-1) | Post-initiation (week=0) | Switch or Add? | Patients | % patients | Rank |
|---|---|---|---|---|---|
| Methotrexate | Adalimumab+Methotrexate | Add | 76 | 8.2% | 1 |
| Methotrexate | Adalimumab | Switch | 63 | 6.8% | 2 |
| None | Adalimumab | From None | 59 | 6.3% | 3 |
| Leflunomide+Methotrexate | Adalimumab+Methotrexate | Switch | 50 | 5.4% | 4 |
| Methotrexate+Sulfasalazine | Adalimumab+Methotrexate+Sulfasalazine | Add | 45 | 4.8% | 5 |
| Leflunomide+Methotrexate | Adalimumab+Leflunomide+Methotrexate | Add | 42 | 4.5% | 6 |
| Methotrexate | Etanercept | Switch | 36 | 3.9% | 7 |
| None | Etanercept | From None | 33 | 3.5% | 8 |
| Methotrexate+Sulfasalazine | Adalimumab+Methotrexate | Switch | 30 | 3.2% | 9 |
| Leflunomide+Methotrexate | Adalimumab | Switch | 28 | 3.0% | 10 |
| Methotrexate+Sulfasalazine | Adalimumab | Switch | 28 | 3.0% | 11 |
| Methotrexate | Etanercept+Methotrexate | Add | 28 | 3.0% | 12 |
| None | Golimumab | From None | 26 | 2.8% | 13 |
| Methotrexate | Golimumab | Switch | 25 | 2.7% | 14 |
| Methotrexate | Golimumab+Methotrexate | Add | 24 | 2.6% | 15 |
| Leflunomide+Methotrexate | Etanercept+Methotrexate | Switch | 20 | 2.2% | 16 |
| Methotrexate+Sulfasalazine | Etanercept+Methotrexate | Switch | 19 | 2.0% | 17 |
| Leflunomide+Methotrexate | Adalimumab+Leflunomide | Switch | 19 | 2.0% | 18 |
| Leflunomide+Methotrexate | Golimumab+Methotrexate | Switch | 15 | 1.6% | 19 |
| Methotrexate+Sulfasalazine | Etanercept+Methotrexate+Sulfasalazine | Add | 14 | 1.5% | 20 |
| Methotrexate+Sulfasalazine | Adalimumab+Sulfasalazine | Switch | 12 | 1.3% | 21 |
| Leflunomide | Adalimumab | Switch | 11 | 1.2% | 22 |
| Leflunomide | Adalimumab+Leflunomide | Add | 11 | 1.2% | 23 |
| Methotrexate+Sulfasalazine | Golimumab+Methotrexate+Sulfasalazine | Add | 11 | 1.2% | 24 |
| Leflunomide+Methotrexate | Etanercept+Leflunomide+Methotrexate | Add | 11 | 1.2% | 25 |
| Methotrexate+Sulfasalazine | Etanercept | Switch | 10 | 1.1% | 26 |
| Leflunomide+Methotrexate | Golimumab | Switch | 9 | 1.0% | 27 |
| Leflunomide | Etanercept+Leflunomide | Add | 7 | 0.8% | 28 |
| Leflunomide+Methotrexate | Golimumab+Leflunomide+Methotrexate | Add | 7 | 0.8% | 29 |
| Sulfasalazine | Etanercept+Sulfasalazine | Add | 7 | 0.8% | 30 |
| Methotrexate | Infliximab+Methotrexate | Add | 6 | 0.6% | 31 |
| Methotrexate+Sulfasalazine | Etanercept+Sulfasalazine | Switch | 6 | 0.6% | 32 |
| Methotrexate+Sulfasalazine | Golimumab+Methotrexate | Switch | 6 | 0.6% | 33 |
| Leflunomide+Sulfasalazine | Adalimumab+Leflunomide+Sulfasalazine | Add | 4 | 0.4% | 34 |
| Sulfasalazine | Etanercept | Switch | 4 | 0.4% | 35 |
| Other | Other | | 250 | 26.9% | |
| Total | | | 930 | 100% | |

Table 3 shows that the most common transition is to add adalimumab to methotrexate. The next two most common transitions were to switch from methotrexate to adalimumab and to initiate therapy on adalimumab without having been on any DMARD at the time.

In total there were 930 patients who initiated bDMARD therapy for psoriatic arthritis in the 12 month period. Of these 121 (13.0%) initiated without having been on any DMARD at the time, 323 (34.7%) added the bDMARD to an existing DMARD regimen and 486 (52.3%) substituted one or more drugs in an existing DMARD regimen.

At initiation 40% of patients were on bDMARD monotherapy and 60% were using a combination of DMARD and bDMARD. Twelve months after initiation 745 of the 930 initiators were still on bDMARD therapy and of these, 42% of patients were on bDMARD monotherapy and 58% were using a combination of DMARD and bDMARD. Thus, over 12 months the proportion of use as monotherapy had increased by the relatively small amount of 2%.

The estimated patient drug regimens in the 18 months prior to and 12 months post initiation to bDMARD therapy for psoriatic arthritis are shown in Figure 3. The patient cohort is the same as that used for the drug regimen transition analysis in Table 3 (i.e. patients who initiated therapy in the 12 month period October 2013 to September 2014, inclusive).

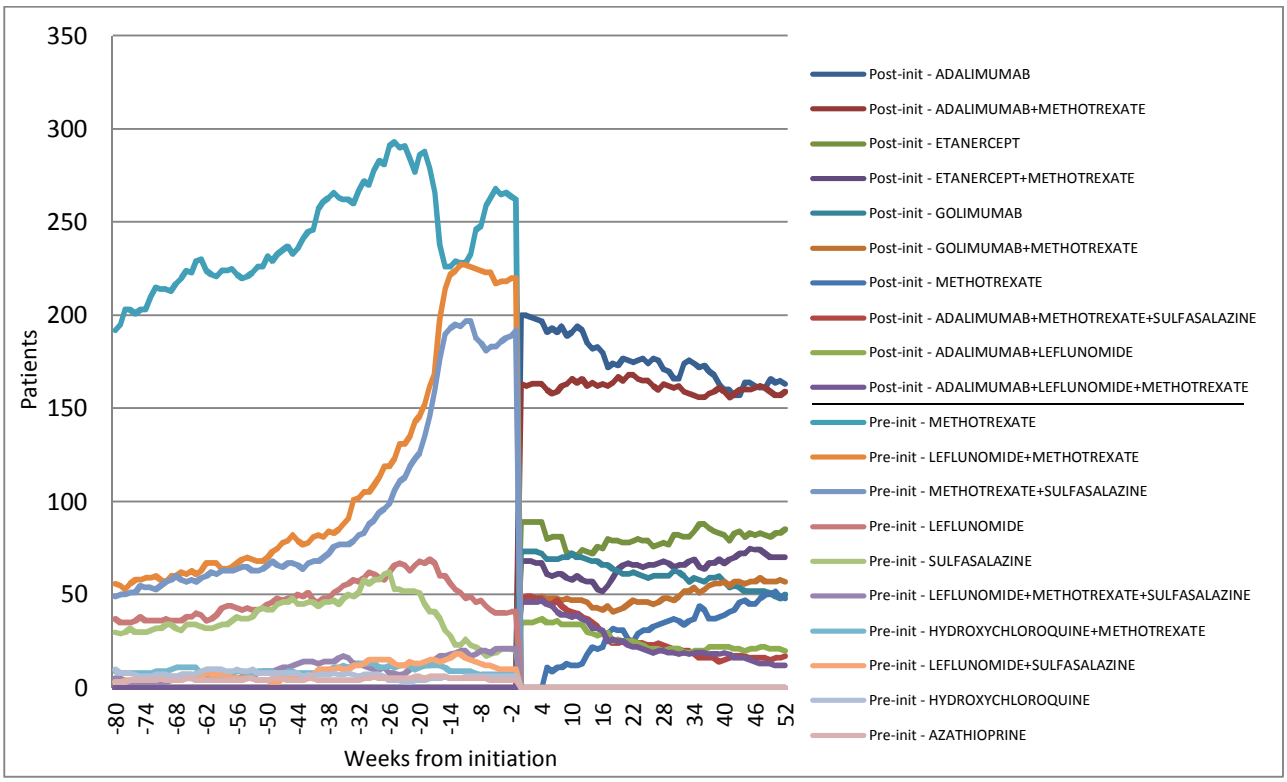


**Figure 3: Estimate drug regimens pre and post initiation to bDMARD therapy for PsA**
Note: for readability, only the 10 most frequent regimens pre and post initiation are shown.

Figure 3 shows that in the weeks before initiation to bDMARD therapy the number of patients on the methotrexate combination therapy with leflunomide and sulfasalazine

increased and the patients on monotherapy of leflunomide and sulfasalazine decreased. This pattern is consistent with the restriction requirement to trial methotrexate and one of leflunomide or sulfasalazine before initiating bDMARD therapy. It can be seen that the combination DMARD therapy started to increase more rapidly about 38 weeks prior to initiation to a bDMARD and increased more rapidly again at about 21 weeks prior. The number of patients on leflunomide and methotrexate peaked at 14 weeks prior and the number on sulfasalazine and methotrexate peaked at 12 weeks prior. These time frames are consistent with the 3 month trial period specified in the restriction.

***Estimated Patient Drug Regimens by calendar week***

Figure 4 shows the estimated drug regimens by calendar week from June 2013 to mid-August 2015 for all regimens that contain a bDMARD for psoriatic arthritis. The analysis includes all patients, not just the 12 month initiator cohort used for the previous analyses.

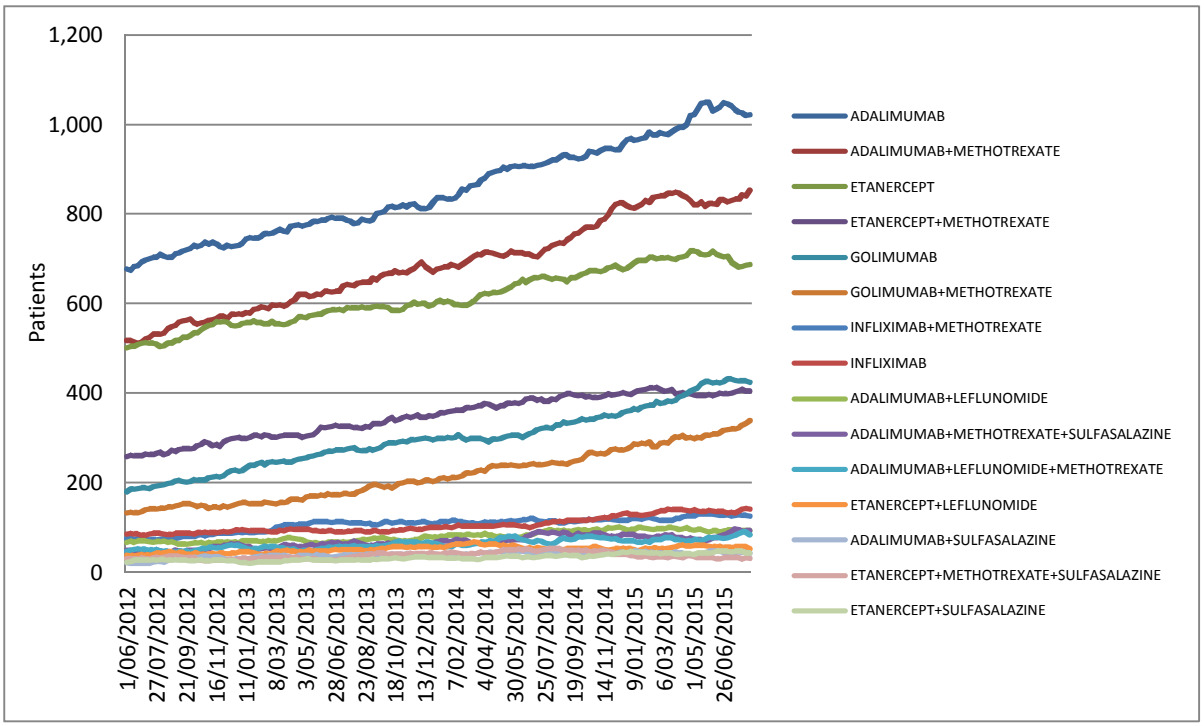


**Figure 4: Estimated drug regimens containing a bDMARD for PsA by calendar week**

Note: for readability, only the 15 most frequent regimens are shown. Date of supply data up to the end of September 2015 are used to construct the prevalent regimens, however Figure 4 only shows regimens up to the end of mid-August 2015 as the last 6 weeks were subject to "end effects" and not displayed, see Appendix A for details.

At the start of the last week in Figure 4 (i.e. 14/8/2015), there were a total of 4,884 patients estimated to be on bDMARD therapy for PsA. 2,314 (47.4%) were estimated to be on bDMARD monotherapy and the remainder (2,570, 52.6%) were estimated to be on a bDMARD in combination with a DMARD. The most common combination was adalimumab+methotrexate (853 patients, 17.5% of all patients).

At the start of the first week in Figure 4 (i.e. 1/6/2012), there were a total of 2,934 patients estimated to be on bDMARD therapy for PsA. 1,444 (49.2%) were estimated to be on bDMARD monotherapy and the remainder (1,490, 50.8%) were estimated to be on a bDMARD in combination with a DMARD. The percentage distribution between mono and combination therapy is similar as at 1 June 2012 and 14 August 2015.

The distribution of top 20 estimated drug regimens containing a bDMARD as at 14 August 2015 is shown in the table below.

**Table 4: Top 20 estimated patient drug regimens containing a bDMARD as at 14/8/2015**

| Estimated drug regimen | Patients | % Patients | Rank |
|---|---|---|---|
| Adalimumab | 1,022 | 20.9% | 1 |
| Adalimumab+Methotrexate | 853 | 17.5% | 2 |
| Etanercept | 688 | 14.1% | 3 |
| Golimumab | 425 | 8.7% | 4 |
| Etanercept+Methotrexate | 405 | 8.3% | 5 |
| Golimumab+Methotrexate | 338 | 6.9% | 6 |
| Infliximab | 141 | 2.9% | 7 |
| Infliximab+Methotrexate | 125 | 2.6% | 8 |
| Adalimumab+Methotrexate+Sulfasalazine | 93 | 1.9% | 9 |
| Adalimumab+Leflunomide | 92 | 1.9% | 10 |
| Adalimumab+Leflunomide+Methotrexate | 84 | 1.7% | 11 |
| Etanercept+Leflunomide | 53 | 1.1% | 12 |
| Adalimumab+Sulfasalazine | 43 | 0.9% | 13 |
| Etanercept+Sulfasalazine | 42 | 0.9% | 14 |
| Certolizumab Pegol | 38 | 0.8% | 15 |
| Golimumab+Leflunomide | 33 | 0.7% | 16 |
| Etanercept+Methotrexate+Sulfasalazine | 31 | 0.6% | 17 |
| Golimumab+Methotrexate+Sulfasalazine | 28 | 0.6% | 18 |
| Certolizumab Pegol+Methotrexate | 26 | 0.5% | 19 |
| Etanercept+Leflunomide+Methotrexate | 26 | 0.5% | 20 |
| Other | 298 | 6.1% | |
| Grand Total | 4,884 | 100.0% | |

Table 4 has a similar ranking to Figure 4, except that certolizumab pegol is in the table (Rank = 15) but not the figure. This is because the ranking in Table 4 is based on the number of patients on a bDMARD containing regimen as at 14/8/2015, whereas the Figure 4 ranking is based on the total patient count across the displayed period. As certolizumab pegol was not listed until 1 September 2014, it is ranked less than 15 in Figure 4 and so does not appear.

## Discussion

The trajectory of DMARD use increased in the 20 weeks prior to initiation to bDMARD therapy. This is consistent with the 3 month trial period specified in the restriction.

Of patients initiating bDMARD therapy in quarter 3 2015, 81.3% (248 of 305 patients) had been supplied methotrexate and sulfasalazine or leflunomide in the 4 years prior to initiation. 18.7% of patients that initiated in this quarter did not appear to have fulfilled the prior DMARD aspect of the restriction criteria.

Sensitivity analysis was undertaken using a look back period of exactly 5 years from each patient's bDMARD initiation date (this was only possible for the three quarters in 2015). The result was 83.0% of patients had been supplied methotrexate and sulfasalazine or leflunomide prior to initiation in 2015 Q3 and so 17.0% of patients did not fulfil the prior DMARD criteria. Thus the addition of an extra year of look back reduced the estimate of patients not fulfilling the prior DMARD criteria by 1.7%. DUSC noted that the 17% figure would increase if the analysis had regard to the treatment duration (ie. at least 3 months) and dose criteria. However, it would decrease slightly if the look back period was extended beyond 5 years.

The percentage of patients trialling none of the restriction specified drugs (methotrexate, sulfasalazine and leflunomide) has slowly increased. In Figure 1 the minimum value for this percentage was 3.4% in 2014 Q2 and the maximum value was 9.9% in 2015 Q2. Differences between the PBS restrictions and clinical guidelines could be a factor contributing to this increase.

At initiation to bDMARD therapy for psoriatic arthritis, 34.7% of patients added the bDMARD to an existing DMARD regimen, 52.3 % of patients substituted one or more drugs in an existing DMARD regimen and 13.0% initiated without having been on any DMARD at the time.

It was estimated that, as of 14 August 2015, 52.6% of prevalent patients on bDMARD therapy for PsA are on bDMARD + DMARD combination therapy and the remainder (47.4%) on bDMARD monotherapy.

## DUSC consideration

It is uncertain what proportion of patients not trialling methotrexate and sulfasalazine or leflunomide may have a contraindication that exempts them from the requirement. Where treatment with methotrexate, sulfasalazine or leflunomide is contraindicated according to the relevant TGA-approved Product Information, details must be provided at the time of application for authority approval. A retrospective assessment of written applications

would be required to determine the proportion of people who are contraindicated or intolerant to therapies.

The Pre-Sub-Committee Response (PSCR) from a Sponsor used existing data to estimate that up to 28% of patients could have a contraindication to at least one of the required DMARD medications.

DUSC considered that:

- Overall it is likely that it is only a minority of patients with psoriatic arthritis (PsA) that do not meet restriction criteria with regard to prior DMARD use. Contraindications for use probably account for many of those without prior adequate DMARD exposure.
- Methotrexate is normally the first DMARD trialled. If a patient has sustained abnormal liver function tests whilst on methotrexate this may be a relative contraindication to leflunomide and sulfasalazine. Thus methotrexate intolerance may be the driver of the observed contraindications to DMARDs.
- Data on contraindications are provided on the written application forms sent to Medicare by the prescriber at initiation.

## DUSC actions

The DUSC requested that;

- the addendum 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

AbbVie Pty Ltd: AbbVie notes that the DUSC analysis is informative and agrees that the percentage of patients not trialling DMARDS due to contraindications is aligned with literature. As noted by the DUSC, written applications are required prior to approval for bDMARD use with stringent eligibility criteria.

Pfizer Pty Ltd: The sponsor has no comment

Janssen-Cilag Pty Ltd: Janssen consider that these analyses conducted by the DUSC demonstrate that the vast majority of PsA patients are receiving the prerequisite disease modifying anti-rheumatic drugs (DMARDs) at the appropriate dose for the minimum durations stipulated in the initial treatment PBS restriction for the biologics. Of those patients who did not receive methotrexate plus either leflunomide or sulfasalazine prior to initiation of a biologic, Janssen consider it highly likely that the vast majority were contraindicated to at least one of these therapies. Overall these analyses further support that biologics are being used appropriately in the population determined to be cost-effective by the PBAC.

UCB Australia 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:
## Detailed methodology to estimate drug regimens and regimen transitions

***Drug treatment regimens are estimated from prescription supply dates***

The prescription data contains date of supply of each prescription, but no information on whether or not medicines should be (or were) co-administered. Thus co-administration was estimated from the data in the following way;

Step 1:

Determine the estimated medication coverage days for **each** drug or drug group.

This mainly involves detecting breaks in treatment. The outcome is the start and estimated end date for each episode of treatment for each drug or drug group.

Step 2:

Determine the estimated medication coverage days **across all** drug and drug group episodes defined in Step 1. The outcome is an estimated treatment regimen for each patient for every day in the data period.

Similar methods have been used for assessing medicine use in Australian populations.[4,5] Hallas[6] describes the method and provides references to early variants.

Figure B.1 illustrates the method specified above. The standard coverage days (SCD) for each drug A, B & C have been shortened to 5 days to enable the figure to fit on one page. The Step 1 process results in the production of the episodes (pink bars) and the Step 2 process results in the production of the treatment regimen (blue bar). The days in this illustration are days from initiation (applicable to an incident patient analysis) but they can also be calendar days (applicable to a prevalent patient analysis).

In this illustration, a break in treatment is defined as a coverage gap of 2 or more SCDs (i.e. the patient has not received re-supply at two consecutive expected refill dates. The first gap in drug A coverage (from days -39 to -35) is not deemed to be a break in the drug A Episode 1 as the estimated gap in coverage is only 1 x SCD. The 2nd gap in drug A coverage from days -29 to -20 is deemed to be a break in treatment and the end of Episode 1 because the gap in estimated coverage is 2 x SCD.

The two prescriptions for drug B supplied on day -9 are interpreted as dose escalation of drug B, if each prescription is for a different strength. The two prescriptions are deemed to

[4] Pratt N, Roughead EE, Ramsay E, Salter A, Ryan P 2011 "Risk of hospitalization for hip fracture and pneumonia associated with antipsychotic prescribing in the elderly: a self-controlled case-series analysis in an Australian health care claims database" Drug Saf. 34(7):567-75. doi: 10.2165/11588470-000000000-00000.

[5] Vitry AI, Roughead EE, Preiss AK, Ryan P, Ramsay EN, Gilbert AL, Caughey GE, Shakib S, Esterman A, Zhang Y, McDermott RA 2010 "Influence of comorbidities on therapeutic progression of diabetes treatment in Australian veterans: a cohort study" PLoS One. 5(11):e14024. doi: 10.1371/journal.pone.0014024.

[6] Hallas J. 2005 "Drug utilization statistics for individual-level pharmacy dispensing data" Pharmacoepidemiol Drug Saf. 14:455–463. doi: 10.1002/pds.1063.

be necessary to supply one SCD period and not used to extend the drug coverage period. If each prescription of drug B were for the same strength then this would be interpreted as "stockpiling" and assumed to extend the drug coverage period (see Details of Methodology below for details)

Drug C is a 3rd line agent and initiated on day 0 (by definition). The basic method imputes a short period of B+C, but a refinement of the method includes the calculation of an adjusted treatment regimen which removes short periods of overlap when it is likely that a switch has occurred before prior medicine is deemed to be fully used.

The final method for estimating the drug treatment regimen includes several refinements which are explained in below. Briefly they are:

1. Calculation of the treatment regimen on a weekly rather than daily basis.
2. Calculation of drug treatment regimen transitions – including an adjustment to allow for switching when the prior medication is not fully used.
3. Adjustment to allow for stockpiling of medication, both same-day supply and supplies on different days.
4. Change in the rules for prescriptions whose coverage spans the initiation data;
   - removal of stockpiling rule
5. Estimating if a patient is continuing or stopping after their last script

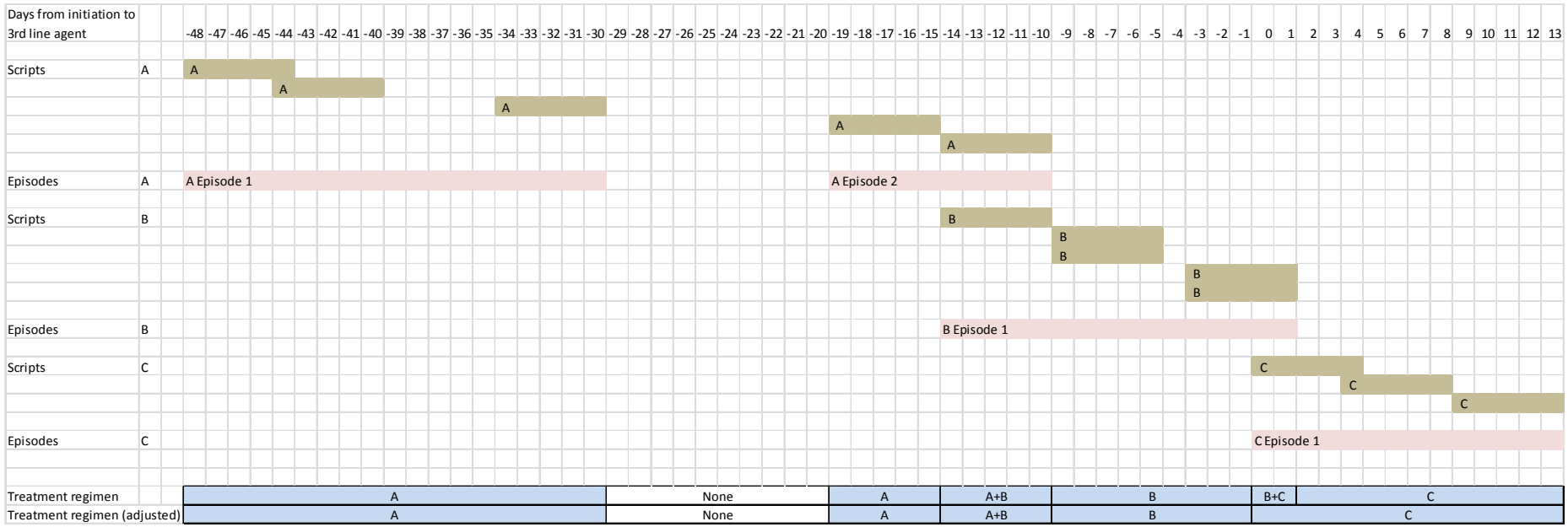


**Figure B.1 Diagrammatic representation of the methodology used to determine treatment regimen**

*Details of Methodology*

**1. Calculation of the treatment regimen**

Drug treatment regimens are estimated from prescription supply dates in the following way;

Step 1:

Determine the estimated medication coverage days for **each** drug or drug group.

This mainly involves detecting breaks in treatment. The outcome is the start and estimated end date for each episode for each drug or drug group.

Step 2:

Determine the estimated medication coverage days **across all** drug and drug group episodes defined in Step 1. The outcome is an estimated treatment regimen for each patient for every day in the data period.

Step 2 above was modified so that the treatment regimen was estimated on a weekly rather than daily basis. This modification was deemed necessary to keep the data volume at a manageable level. This modification means that if the a medication coverage start date falls in a particular calendar week (for prevalent patient analysis) or week since initiation (for initiation analysis) then the medication is deemed to cover that week. The same rule was applied to the medication coverage end date.

**2. Drug regimen transitions - including an adjustment to allow for switching when the prior medication is not fully used**

Once estimated drug regimens have been determined for every week, then transitions can be computed.

These are useful for determining patient behaviour upon initiation of a drug; e.g. A→A+B (adding to existing therapy), A→B (switching) or None→A (starting therapy).

The transitions can be;

A. previous drug regimen →drug regimen at week x, or
B. drug regimen at week -1 →drug regimen at week x

Option A has the advantage that it can be calculated at any week, whereas Option B can only be calculated after initiation (i.e. from week 0). The main advantages of Option B are that it can easily be used to adjust the drug regimen in the first few weeks after initiation to allow for switching when the prior medication is not fully used. That is, if a patient switches from A to B, in the first few weeks after initiation to drug B the drug regimen may be incorrectly estimated to be A+B if the patient still has drug A "on hand" (i.e. some is unused) when drug B is initiated.

The regimen transitions are adjusted so that if a regimen transition corresponding to a switch (e.g. A→B) is detected within the first X weeks after initiation (e.g. at week Y), then all weeks between the initiation (i.e. week 0) and week Y are modified to the switch transition (i.e. A-B). This means some instances of "A→A+B" (apparent co-administration after a switch) are modified to "A→B" from week 0 to week Y (where Y ≤ X). The value of X is the 1 week + SCD (expressed in weeks) for the drug or drug group that is being substituted.

This means that if a drug A was supplied 1 day before an initiation to drug B and then there were no further supplies of drug A, then there would be apparent co-administration of A and B from week 0 to week X-1 and in week X the drug regimen would be drug B only and considered a switch. Thus the regimens from weeks 0 to X-1 would be modified to be dug B only. If a switch is first detected in week X +1 then the A script would have been supplied in week 0 (i.e. at or after initiation to drug B) and this would mean that the transition was not a switch, but an add. Thus the logic is only applied to weeks 0 to X.

A transition is considered a switch if a drug in the regimen prior to initiation (the week=-1 regimen) is not in the regimen post initiation (i.e. the week=0 regimen).

After this transition adjustment, the drug regimens can also be adjusted by using the regimen after the arrow in the adjusted regimen transition. That is, if a transition gets adjusted from A→A+B to A→B in week Y then the adjusted drug regimen for week Y changes from A+B to B. Thus even though the drug regimen is calculated first, its adjustment is dependent on both the regimen transition and adjusted regimen transition. Thus the sequence of calculations is;

1. drug regimens
2. drug regimen transitions around initiation
3. adjusted drug regimen transitions
4. adjusted drug regimens

The above adjustment process is reliant on having regard to drug initiations. If the analysis is for prevalent drug regimens only (i.e. regimens by calendar week and not relative to an initiation date) then the above adjustment is not possible. This is not a major problem as the overestimation of co-administration (e.g. A→A+B instead of A→B) is greatest in the month after initiation. In a prevalent patient analysis, patient initiations (to any and all drugs) are spread out in time (i.e. all patients do not generally initiate in the same week), and so the overestimation is also spread out over time and so minimised. In an initiating patient analysis, all over-estimations occur at the same time (as time is relative to the initiation week) and so the overestimation is significant and so needs to be adjusted for. In theory in a prevalent patient analysis, it is possible to do an initiation analysis for every drug and so find adjusted drug regimens that can then be re-expressed in calendar weeks. In practice this is too resource intensive and is unlikely to be make a significant difference to the prevalent patient drug regimens.

### 3. Adjustment to allow for stockpiling of medication, both same-day supply and supplies on different days

The two step methodology outlined in point 1 and refined by logic in point 2 above did not take into account the phenomenon of stockpiling. This often occurs towards the end of the calendar year when a Safety Net card holder fills prescriptions more frequently than expected, so as to stockpile the medicine and avoid a higher co-payment in the next calendar year when they lose Safety Net eligibility. Stockpiling can also occur at other times of the year. Step 1 can impute higher rates of breaks in episodes around February. This is likely to be due to the stockpiling effect and not due to genuine breaks in treatment. Thus the rule to estimate the prescription coverage end date was modified to be the greater of;

- the predicted coverage end date of the previous prescription plus the standard coverage days (SCD); and,
- the actual refill date of the previous prescription plus the SCD.

This way of calculating the prescription coverage end date takes into account medication stockpiling (i.e. early supply). The logic of the break rule remained unchanged, that is;

- a break was where a prescription was supplied 2 x SCD or more after the coverage end date of the previous prescription for the same drug or drug group.

Application of this refinement results in the reduction of the extent of seasonality in the number of breaks in episodes.

If multiple prescriptions of the same drug (but not the same strength) or drug group are supplied on the same day, it was assumed that these were necessary for the prescribed dose for the SCD and not for an extension of coverage.

If multiple prescriptions of the same drug are supplied it is generally for two different strengths to enable the prescribed dose to be administered. If two prescriptions for the same strength (as opposed to increased quantity for a single script) are supplied, the method assumes this is similar to stockpiling (i.e. same day stockpiling) and the predicted coverage end date is extended to be the greater of;

- the predicted coverage end date of the previous prescription plus n x SCD; and,
- the actual refill date of the previous prescription plus n x SCD

where n = number of prescriptions on the same day.

A special case of multiple prescriptions being supplied on the same day is Regulation 24 prescriptions.

If the original and repeat prescriptions were supplied under Regulation 24 on the same day, then this was assumed to extend the coverage period (i.e. coverage period = prescriptions x SCD).

**4. Change in the rules for prescriptions whose coverage spans the initiation data; - removal of stockpiling rule**

It was found that the stockpiling rule could result in the script coverage end date getting considerably ahead of the script supply date. This is the intent of the rule, however when a new drug B was initiated the stockpiling rules was resulting in the imputation that the new

drug B was being added to an existing drug A, when in all probability it was substituting drug A. To correct for this, the script coverage rule was changed so that if the script coverage period for a drug A script included the initiation date for drug B, then the stockpiling rule would not apply to the drug A script (i.e. its coverage would be from its supply date to the supply date + SCD). The rationale for this change is that even if patient has a lot of drug A on hand, the decision by the prescriber to initiate a new drug means that a switch could have occurred.

## 5. Estimating if a patient is continuing or stopping after their last script

If the last script in a patients script history is supplied within 2 x SCD of the end of the data period then the treatment is estimated to be continuing at the end of the data period (i.e. the episode coverage end date is set to the end date of the data period). Otherwise the treatment episode is estimated to have stopped and the episode coverage end date is equal to If the last script in a patients script history plus 1 x SCD.

**Table B.1: Standard Coverage Days used in this analysis**

| Drug or Drug Group | Standard Coverage Days (i.e. Median time to re-supply by any item of the same drug or drug group) |
|---|---|
| Adalimumab | 29 |
| Azathioprine | 41 |
| Certolizumab Pegol | 21 |
| Cyclosporin | 35 |
| Etanercept | 29 |
| Golimumab | 30 |
| Hydroxychloroquine | 55 |
| Infliximab | 56 |
| Leflunomide | 32 |
| Mercaptopurine | 88 |
| Methotrexate | 133 |
| Sulfasalazine | 52 |

If the drug regimens are display by calendar week instead of weeks relative to initiation, then towards the end of the data period there may be some obvious “end effect” artefacts in some of the regimen time series. This is because the true continuation rate may not be well estimated by the continuation logic described above (i.e. If the last script is supplied within 2 x SCD of the end of the data period then the treatment is estimated to be continuing at the end of the data period). If this is the case then there will be a trend change close to the end of the regimen time series plot. One solution to this problem is to not display approximately the last 2 x SCD portion of the time series.