# bDMARDs for ankylosing spondylitis: utilisation analysis

## Drug utilisation sub-committee (DUSC)

***February 2016***

## Abstract


***Purpose***

To examine the PBS use of biological disease modifying anti-rheumatic drugs (bDMARDs) used to treat ankylosing spondylitis.

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

- Infliximab: 1 August 2004
- Etanercept: 1 April 2005
- Adalimumab: 1 March 2007
- Golimumab: 1 August 2010
- Certolizumab pegol: 1 September 2014

***Data Source / methodology***

The Department of Human Services (DHS) Authority Approvals database was used for most patient level analyses (eg. patient counts, continuation rates and drug sequence). The DHS prescription claims database and the DUSC Highly Specialised Drugs database were used for prescription count and expenditure analyses.

***Key Findings***

- The number of patients on bDMARD treatment for ankylosing spondylitis (AS) has increased from the time of listing, from 628 in 2005 to 6,106 in 2014 with no indication of plateauing.
- The number of patients initiating bDMARD treatment for AS per year has increased from 453 in 2005 to 1,190 in 2014. Each time a new drug is listed on the PBS there was a slight step up in the number of initiating patients followed by a plateauing. This may be influenced by patient access programs and grandfathering of patients to PBS subsidised supply following listing.
- Adalimumab is the most commonly used bDMARD, followed by etanercept and golimumab. Infliximab has low and stable use. Certolizumab pegol was only recently listed and has yet to establish market share.
- Treatment continuation is high with 69-84% of new patients receiving a second authority approval for their initial bDMARD, and 91% receiving a second approval for

any bDMARD. This is higher than anticipated based on response rates in the key clinical trials.
- The majority of people remain on bDMARD therapy for long durations. For example, 72% of patients who began treatment in 2009 have received at least 10 authority approvals.
- 62% of patients who commenced bDMARD therapy prior to 2014 have received an authority for a single bDMARD, with 27% receiving authority approvals for two bDMARDs, 9.2% for three bDMARDs, and 2.2% for more than three bDMARDs.
- Commonwealth expenditure on bDMARDs for ankylosing spondylitis has increased each year, reaching $107.4 million in 2014.

# Background

## Pharmacology

Adalimumab, etanercept, golimumab, infliximab and certolizumab pegol are biologic therapies that bind to tumour necrosis factor (TNF-alpha) or its cell surface targets and inhibit its inflammatory action. [1,2,3,4,5]

## Therapeutic Goods Administration (TGA) approved indications

Adalimumab is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Certolizumab pegol is indicated in the treatment of adult patients with active ankylosing spondylitis who have been intolerant or had inadequate response to at least one non-steroidal anti-inflammatory drug (NSAID).

Etanercept is indicated for the signs and symptoms of active ankylosing spondylitis in adults.

Golimumab is indicated for the treatment of active ankylosing spondylitis in adults.

Infliximab is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active ankylosing spondylitis.

All of the drugs are also indicated for the treatment of other inflammatory conditions.

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[1] Adalimumab (Humira®), Australian Approved Product Information. Sydney: AbbVie Pty Ltd. Approved 10 December 2003, updated 31 August 2015. Available from <https://www.ebs.tga.gov.au/>
[2] Certolizumab pegol (Cimzia®), Australian Approved Product Information. Melbourne: UCB Australia Pty Ltd. Approved 20 January 2010, updated 24 February 2015. Available from <https://www.ebs.tga.gov.au/>
[3] Etanercept (Enbrel®), Australian Approved Product Information. Sydney: Pfizer Australia Pty Ltd. Approved 8 September 2000, updated 7 December 2015. Available from <https://www.ebs.tga.gov.au/>
[4] Golimumab (Simponi®), Australian Approved Product Information. Sydney: Janssen-Cilag Pty Ltd. Approved 13 November 2009, updated 7 July 2014. Available from <https://www.ebs.tga.gov.au/>
[5] Infliximab (Remicade®), Australian Approved Product Information. Sydney: Janssen-Cilag Pty Ltd. Approved 2 August 2000, updated 11 February 2015. Available from <https://www.ebs.tga.gov.au/>

## Dosage and administration

**Table 1: Dose and administration of bDMARDs for ankylosing spondylitis[6]**

| Drug, brand name and sponsor | Dose and frequency of administration |
|---|---|
| Adalimumab<br>Humira®, AbbVie Pty Ltd | 40mg solution in pre-filled syringe or cartridge for once-fortnightly subcutaneous administration. |
| Certolizumab pegol<br>Cimzia®, UCB Australia Pty Ltd | 200mg/mL solution in pre-filled syringe for fortnightly subcutaneous administration.<br>Loading dose of 400mg (2 subcutaneous injections) at weeks 0, 2 and 4. |
| Etanercept<br>Enbrel®, Pfizer Australia Pty Ltd | 25mg solution in pre-filled syringe for twice-weekly subcutaneous administration.<br>50mg solution for injection, as pre-filled syringe or cartridge for auto-injector for once-weekly subcutaneous administration. |
| Golimumab<br>Simponi®, Janssen-Cilag Pty Ltd | 50mg solution for injection, as pre-filled syringe or injection pen for once-monthly subcutaneous administration. |
| Infliximab<br>Remicade®, Janssen-Cilag Pty Ltd<br>Inflecta®, Hospira Pty Ltd | 5mg/kg given as IV infusion followed by 5mg/kg doses at 2 and 6 weeks after initiation, then every 6 weeks after. |

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

[6] Source: adalimumab (Humira®) Product Information, accessed 2 July 2015; certolizumab pegol (Cimzia®) Product Information, Accessed 2 July 2015; etanercept (Enbrel®) Product Information, accessed 2 July 2015; golimumab (Simponi®) Product Information, accessed 2 July 2015; infliximab (Remicade®) Product Information, accessed 18 December 2015.

## PBS listing details (as at 1 December 2015)

**Table 2: Summary of PBS listed bDMARDs for ankylosing spondylitis**

| Name | Item Codes | Forms and strengths | Qty and Rpts | DPMQ | Brand name and manufacturer |
|---|---|---|---|---|---|
| ADALIMUMAB | Initial:<br>9077R; 9103D;<br>Continuing:<br>9078T; 9104E | 40mg/0.8mL injection, 2x 0.8mL<br>Available as syringe or cartridge | Max Qty: 1<br>Repeats:<br>Initial: 3<br>Cont: 5 | $1763.56 | Humira®<br>AbbVie Pty Ltd |
| CERTOLIZUMAB PEGOL | 10137M | 200mg/mL injection, 2x 1mL syringes | Max Qty: 1<br>Repeats: 5 | $1698.16 | Cimzia®<br>UCB Australia Pty Ltd |
| ETANERCEPT | Initial:<br>8778B; 9085E; 9455P<br>Continuing:<br>8779C; 9086F; 9456Q | 25mg injection (4x 25mg vials) & inert substance diluent (4x 1mL syringes)<br>50mg injection (4x 25mg vials) & inert substance diluent (4x 1mL syringes)<br>50mg injection in 1mL single use auto-injector | Max Qty:<br>25mg: 2<br>50mg: 1<br>Repeats:<br>Initial: 3<br>Cont: 5 | $1763.55 | Enbrel®<br>Pfizer Australia Pty Ltd |
| GOLIMUMAB | Initial:<br>3434R; 3435T<br>Continuing:<br>3436W; 3437X | 50mg/0.5mL injection,<br>1x 0.5mL syringe | Max Qty: 2<br>Repeats:<br>Initial: 3<br>Cont: 5 | $1766.48 | Simponi®<br>Janssen-Cilag Pty Ltd |
| INFLIXIMAB[7] | S100 Public Hospital:<br>5753T<br>S100 Private Hospital:<br>6448J | 100mg injection, 1x 100mg vial | Max Qty: 1<br>Repeats: 0[8] | Public Hospital:<br>$574.85<br>Private Hospital:<br>$604.77 | Remicade®<br>Janssen-Cilag Pty Ltd |

Source: the PBS website. Abbreviations: Qty = Quantity; Rpts = Repeats; DPMQ = Dispensed price maximum quantity; Cont = Continuing; S100 = Available under Section 100 special arrangements

### *Restriction (abridged)*

<u>Restrictions for initiating treatment:</u>

There are two initial restrictions for patients commencing therapy on biological medicines for ankylosing spondylitis: Initial 1, for patients new to therapy or commencing a new treatment cycle; and Initial 2, for patients switching therapy within a treatment cycle.

[7] An infliximab biosimilar product (Inflectra®) was listed on 1 December 2015 resulting in a DPMQ reduction from $751.70 to $574.85 (Public Hospital) and from $788.70 to $604.77 (Private Hospital)

[8] The prescriber sets the number of repeats when requesting the authority approval. An original prescription plus 3 repeats (ie. 4 vials) are required to complete the maximum 18 weeks of treatment under the initial treatment phase in the PBS restriction

A treatment cycle is the period where patients have either failed or ceased to sustain a response to three PBS subsidised bDMARDs, and must have, at minimum, a 5 year break in PBS-subsidised biological therapy. Patients who complete a treatment cycle and wait the requisite timeframe are considered to be initiating (Initial 1) patients if they recommence therapy. Both types of initial restriction are shared under single PBS item numbers for each medicine.

For patients initiating therapy for all drugs listed in Table 1 under the Initial 1 restriction, patients must have diagnostically confirmed ankylosing spondylitis and meet the following criteria:

- Treatment is to be initiated by a rheumatologist;
- Patients must have radiographically (plain X-ray) confirmed Grade II bilateral sacroiliitis or Grade III unilateral sacroiliitis;
- Patients must have at least two of the following:
    - Low back pain and stiffness for 3 or more months that is relieved by exercise but not by rest;
    - Limitation of motion of the lumbar spine in the sagittal and frontal planes as determined by a score of at least 1 on each of the lumbar flexion and lumbar side flexion measurements of the Bath Ankylosing Spondylitis Metrology Index (BASMI); or
    - Limitation of chest expansion relative to the normal values for age and gender;
- Patient must have failed to achieve an adequate response following treatment with at least 2 non-steroidal anti-inflammatory drugs (NSAIDs), whilst completing an appropriate exercise programme for a total period of three months.

Consideration may be given if patients are contraindicated to NSAID treatment, by means of written application.

For patients commencing therapy under the Initial 2 (change or recommencement for all patients) restriction, patients must have a documented history of ankylosing spondylitis, have received prior PBS-subsidised bDMARD treatment for this condition in this treatment cycle and have not already failed or ceased to respond to treatment with that bDMARD during the treatment cycle.

Patients are able to access a maximum of 16 weeks treatment for adalimumab, etanercept and golimumab, 18-20 weeks for certolizumab pegol (depending on dosage regimen), and up to 18 weeks treatment with infliximab under this restriction.

<u>Restrictions for continuing treatment:</u>

To be eligible for ongoing treatment for all therapies, patients are required to demonstrate an adequate response to treatment defined as:

- An improvement from baseline of at least 2 on the BASDAI scale and at least 1 of:
    - An erythrocyte sedimentation rate (ESR) of ≤25mm/hr; or
    - C-reactive protein (CRP) of ≤15mg/L; or
    - A minimum reduction of 20% of ESR or CRP from baseline levels.

Continuing treatment authority approvals provide up to 24 weeks of treatment.

There is no provision in the restriction for a break in treatment. The restriction contains the following paragraphs.

*All applications for continuing treatment with this drug must include a measurement of response to the prior course of therapy. This assessment must be submitted no later than 4 weeks from the cessation of that treatment course. If the application is the first application for continuing treatment following an initial treatment course it must be made following a minimum of 12 weeks of treatment with this drug. If the response assessment is not submitted within these timeframes, the patient will be deemed to have failed this course of treatment.*

*Patients who fail to demonstrate a response to treatment with this drug under this restriction will not be eligible to receive further PBS-subsidised treatment with this drug in this treatment cycle. Patients may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised bDMARD was approved in this cycle and the date of the first application under a new cycle.*

There is a limit of three different bDMARDs in a treatment cycle. The notes section of the restriction states;

*Once a patient has either failed or ceased to respond to treatment 3 times, they are deemed to have completed a treatment cycle and they must have, at a minimum, a 5-year break in PBS-subsidised bDMARD therapy before they are eligible to commence the next cycle. The 5-year break is measured from the date of the last approval for PBS-subsidised bDMARD treatment in the most recent cycle to the date of the first application for initial treatment with a bDMARD under the new treatment cycle.*

For an example of a full restriction text for listings, refer to the initial treatment item for adalimumab and the continuing treatment item for adalimumab.

For details of the current PBS listings refer to the PBS website.

***Date of listing on PBS for ankylosing spondylitis***

- Infliximab: 1 August 2004
- Etanercept: 1 April 2005
- Adalimumab: 1 March 2007
- Golimumab: 1 August 2010
- Certolizumab pegol: 1 September 2014

***Changes to listing***

Infliximab and etanercept were first listed with a single initial restriction, which was split into initial 1 and initial 2 restrictions on 1 August 2008. These were applied to all subsequently listed bDMARDs.

The clinical criteria for all bDMARDs, including BASDAI scores, prior use of NSAIDs and ongoing ESR and CRP measurements have not changed since the first listing of infliximab.

All bDMARDs for ankylosing spondylitis were listed with grandfathering restrictions that were removed after several years from each bDMARD. The grandfathering restrictions are still current for golimumab and certolizumab pegol.

There have been a number of minor restriction text changes as new medicines have become available, and the listing of new presentations such as auto-injectors.

Current PBS listing details are available from the PBS website.

## Clinical Guidelines

The Australian Rheumatology Association's (ARA) published recommendations for the use of biologicals for the treatment of ankylosing spondylitis recommend clinicians consider a number of factors when determining appropriate treatment regimens. The ARA acknowledges that its recommended indications and criteria differ from the current eligibility for PBS-subsidised bDMARDs. The most recent advice on the use of bDMARDs differs in the following key ways from the PBS restrictions[9]:

- The initiation criteria in the guidelines are "TNFIs (Tumour necrosis factor inhibitors) should be given to AS patients with persistently high disease activity, (BASDAI $\geqq$4) who have failed conventional treatments according to ASAS (Assessment in Ankylosing Spondylitis Working Group) recommendations". The PBS restriction initiation criteria were summarised on page 6 of this report. The only common element between the two sets of criteria is the requirement to have failed to achieve response with NSAIDs.
- In the guidelines, lack of response to a bDMARD is defined as 50% improvement or 2 point improvement of baseline BASDAI when assessed between 6-12 weeks. The guidelines do not recommend the use of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels when assessing ankylosing spondylitis. The PBS restriction defines an adequate response as an improvement from baseline of at least 2 of the BASDAI and 1 of an ESR < 25 mm per hour; or a CRP < 10 mg per L; or ESR or CRP reduced by at least 20% from baseline.

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

Infliximab: In December 2003, the PBAC accepted the submission's claims for clinical effectiveness and cost-effectiveness, but deferred its final decision to allow consultation between the stakeholders to address uncertainty regarding the wording of the restriction for PBS listing, for consideration at the March 2004 PBAC meeting. In March 2004, the PBAC recommended the listing of infliximab for ankylosing spondylitis on the basis of acceptable cost-effectiveness, noting that the reasons for deferral at the December 2003 meeting (specifically, the development of an appropriate restriction) had now been satisfactorily addressed.

Etanercept: Recommended at the July 2004 PBAC meeting on a cost-minimisation basis with infliximab.

[9] Australian Rheumatology Association (2011), Updated Recommendations for the Use of Biological Agents for the Treatment of Rheumatic Diseases. Available at: https://rheumatology.org.au/downloads/FINAL-BiologicalRecommendations060111_000.pdf Accessed July 6 2015.

Adalimumab: Recommended at the November 2006 PBAC meeting on a cost-minimisation basis with etanercept. The PBAC considered that the rules regarding interchangeability be similar to existing bDMARD switching rules in place for rheumatoid arthritis and psoriatic arthritis.

Golimumab: Recommended at the March 2010 meeting, on a cost-minimisation basis with etanercept.

Certolizumab pegol: Recommended at the March 2014 meeting on a cost-minimisation basis with adalimumab.

At the July 2014 meeting, the PBAC deferred a decision on whether to recommend a change to the second and subsequent continuing treatment authorities for golimumab and infliximab from complex written authority to telephone authority items, pending the outcomes of a post-market review into PBS Authorities.

***Approach taken to estimate utilisation***

The submissions for infliximab and etanercept took an epidemiological approach to estimate utilisation. Submissions estimates for adalimumab, golimumab and certolizumab were based on a market share approach.

Key assumptions in the infliximab for ankylosing spondylitis submission to the December 2003 PBAC were;

Key assumptions in the etanercept for ankylosing spondylitis submission to the July 2004 PBAC were;

- A 0.1% prevalence of ankylosing spondylitis in the Australian population;
- A 0.0069% incidence rate of ankylosing spondylitis in the Australian population;
- 5% of ankylosing spondylitis patients will be suitable for treatment with a TNF inhibitor;
- 100% of eligible patients will commence treatment with etanercept;
- A discontinuation rate of 4% for non-efficacy reasons per year during the initial 12-16 weeks for new patients; and
- 53% of patients will meet the criteria to continue treatment.

## Previous reviews by the DUSC

The DUSC reviewed the utilisation of bDMARDs for ankylosing spondylitis at the February 2009 meeting. The review found that initial approvals for adalimumab had almost immediately exceeded those for etanercept. Infliximab had consistently taken a smaller

market share for this indication for the entire period of listing. First time continuations were found to be in the range of 65-80%.

# Methods

PBS and RPBS prescription approvals for the bDMARD medicines were extracted from the Department of Human Services (DHS) PBS Authority Approval database for the period August 2004 (month of listing of the first bDMARD, infliximab) to September 2015 inclusive, based on the date that the prescription was approved.

The DHS Authority Approvals database was used to determine the number of patients, proportion of patients continuing treatment after their initial course of therapy, and the sequence of bDMARD use.

The number of prevalent patients was determined by counting the number of person specific numbers (non-identifying) in the authority approval data for the specified time period. Authority approvals data was used rather than prescription supply data as the latter is incomplete with respect to patient level supply history for infliximab prior to July 2013. As infliximab is part of the Highly Specialised Drugs (HSD) Schedule, some utilisation data are missing from the DHS prescription database prior to July 2013 because it was processed via an offline system that did not record the data at the prescription and patient level. The analysis period for patient counts was “per calendar year” because it was assumed that patients would receive at least one approval a year as no more than 24 weeks of treatment is approved at a time for ankylosing spondylitis.

The DHS prescription claim database was used for the number of dispensed prescriptions and expenditure. Due to the infliximab data limitation the DUSC Highly Specialised Drugs Database was used to supplement the data. This database combines Public Hospital prescribed offline processed data with Public and Private Hospital prescribed online processed data to give a complete picture of HSD drug utilisation.

Patient counts for more recent periods were done using prescription data from the DHS prescription claims database. These data are complete for infliximab from July 2013 and enable reporting of prevalent patients using a shorter time period (i.e. quarter) because a patient is expected to have a prescription every month. These data are presented in Appendix A to determine the uptake trend of certolizumab pegol (listed 1 August 2014) which was not possible using the annual patient counts based on the Authority Approval data.

### *Number and Sequence of bDMARDs*

The analysis counted patients who received their first bDMARD approval before 1 January 2014. When this analysis was performed the authority approval data was complete until the end of November 2015 (based on date of approval), thus each patient had a minimum follow up period of 23 months to receive authority approvals for alternative bDMARDs. The follow up period was limited to a maximum of 5 years from each patient’s first bDMARD approval. This means that patients who initiated prior to December 2010 had their approval history truncated at 5 years post initiation.

Certolizumab pegol (listed on 1 September 2014) approvals for this cohort were included in the analysis. This means that patients who initiate therapy on certolizumab are not included in the analysis but patients who switch to certolizumab pegol are included.

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.[10]

[10] 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

### *Prescription Counts*

Figure 1 shows the total number of prescriptions dispensed for the five bDMARDs listed on the PBS for ankylosing spondylitis up until the end of September 2015. As infliximab is listed in Section 100, data on prescriptions supplied in public hospitals was only available from quarter 3 2013. Prior to this the number of public hospital prescriptions was estimated based on the number of packs recorded in the DUSC HSD database.

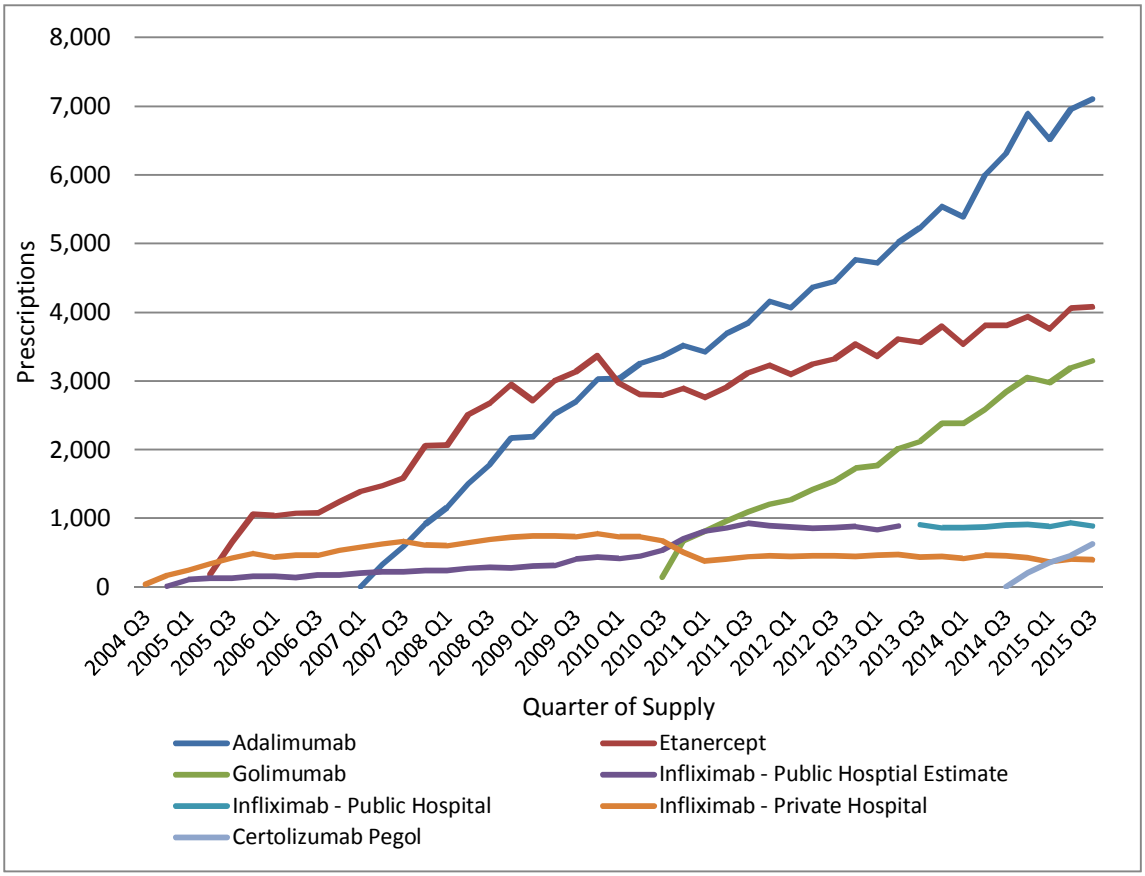


**Figure 1 – bDMARD prescriptions for ankylosing spondylitis, 2004-2015**

Source: DHS Prescription database, and DUSC HSD database for infliximab packs prior to 2013 Q3 which were used to estimate infliximab prescriptions, extracted September 2015

The figure shows sharp increases for etanercept, adalimumab, golimumab and certolizumab pegol in the period immediately after their listing. The increases have continued for adalimumab and golimumab. The number of etanercept prescriptions decreased in the period immediately before the listing of golimumab, and has increased at a slower rate since that time.

***Number of patients***

Figure 2 provides the number of new and prevalent patients receiving bDMARD treatment for ankylosing spondylitis per calendar year since listing on 1 August 2004.

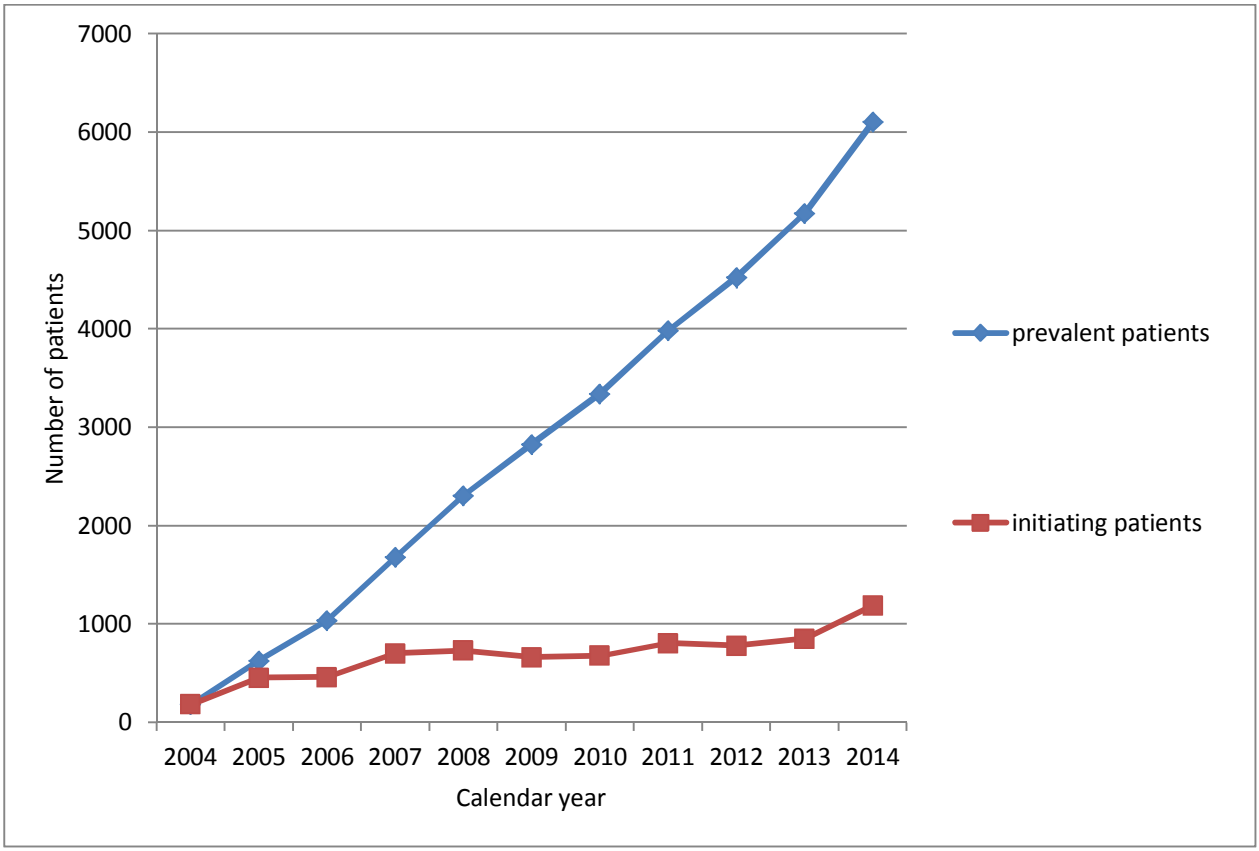


**Figure 2 – New and prevalent patients receiving bDMARD treatment by year**

Source: DHS Authority Approvals database, extracted August 2015

The figure shows an increasing number of prevalent patients receiving bDMARD therapy, with no signs of plateauing. The number of patients initiating bDMARD treatment for AS per year has increased from 453 in 2005 to 1,190 in 2014. Each time a new drug is listed on the PBS there is a slight step up in the number of initiating patients followed by a plateauing. This may be influenced by patient access programs and grandfathering of patients to PBS subsidised supply following listing.

Figure A.1 in Appendix A shows an alternative version of Figure 2 using quarterly data based on supplied prescriptions to give a more detailed picture of the recent trends in 2014 and 2015. The initiating patient increase in 2014 does not appear to be as pronounced in the quarterly data.

Figure 3 provides the number of patients initiating bDMARD therapy for AS by the drug used to initiate therapy.

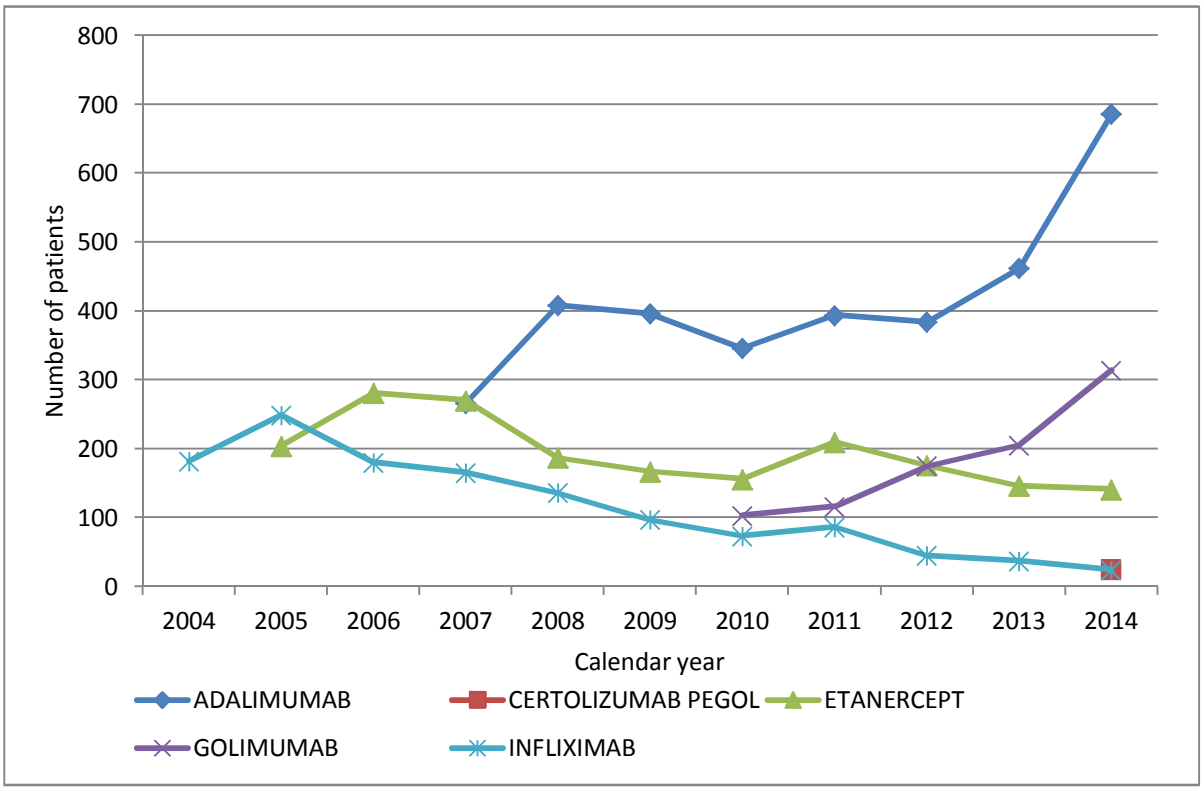


**Figure 3 – bDMARD therapy initiations for ankylosing spondylitis by drug used to initiate therapy**

Source: DHS Authority Approvals Database, extracted August 2015

The number of patients initiating a bDMARD for AS on adalimumab or golimumab has increased substantially. The number of patients initiating on etanercept started to decline when adalimumab was listed. The number initiating infliximab has decreased over time as more subcutaneous bDMARDs, with less frequent dosing, were listed.

Figure A.2 in Appendix A shows an alternative version of Figure 3 using quarterly data based on supplied prescriptions to give a more detailed picture of the recent trends in 2014 and 2015. It can be seen that the increase in therapy initiations on adalimumab and golimumab occurred just prior to the listing of certolizumab pegol in 2014 Q3.

Figure 4 presents the number of prevalent patients on a bDMARD for AS at any time in the calendar year. As patients may be treated with more than one bDMARD in any year, adding patient numbers across drugs will double count some patients. The correct number of total prevalent patients is shown in Figure 2.

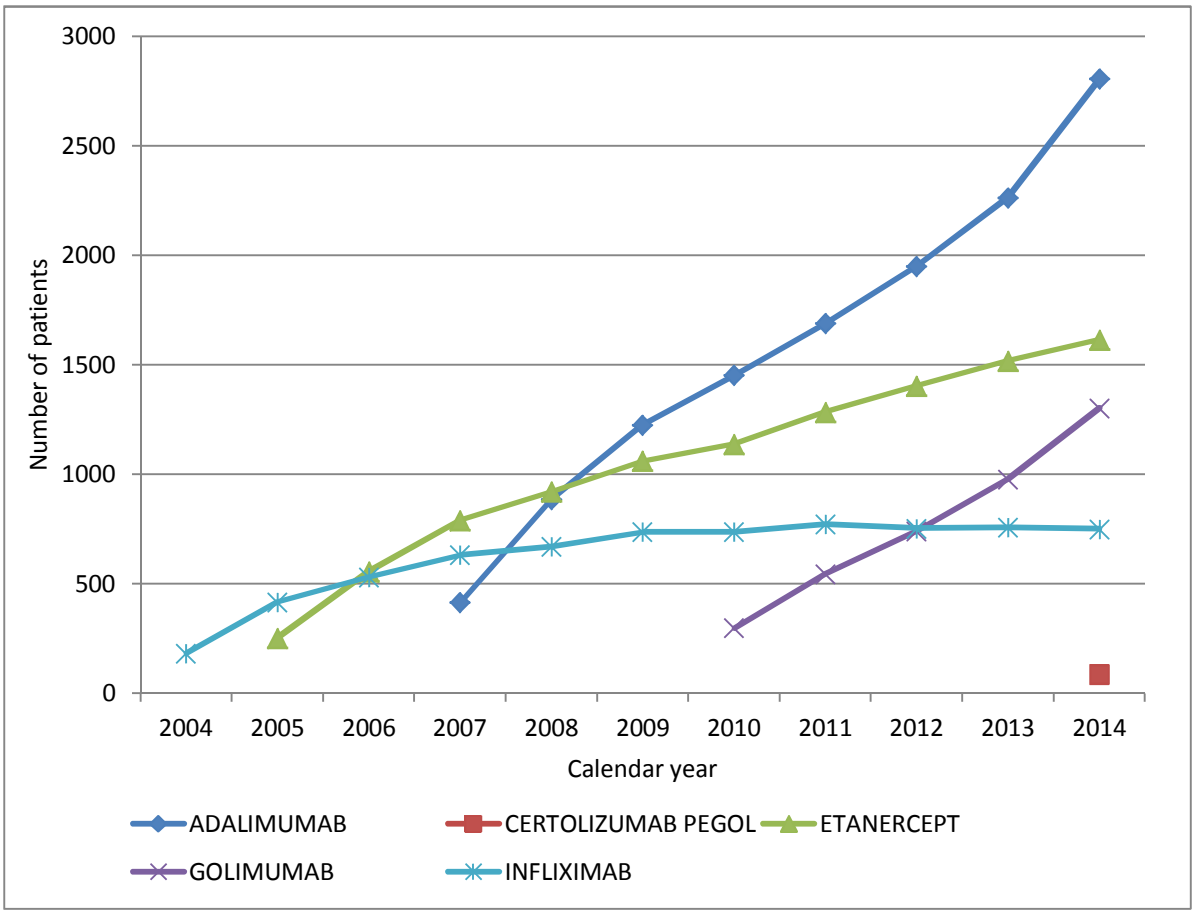


**Figure 4 – Prevalent patients by bDMARD and year**

Source: DHS Authority Approvals database, extracted August 2015.

The number of patients receiving authorities for all bDMARDs except infliximab, continue to rise and show no signs of plateauing.

Figure A.3 in Appendix A shows an alternative version of Figure 3 using quarterly data based on supplied prescriptions to give a more detailed picture of the recent trends in 2014 and 2015. It shows that the prevalent patient trends of the other drugs do not appear to have been impacted by the listing of certolizumab pegol on 1 September 2014.

***Patient Age and Gender analysis***

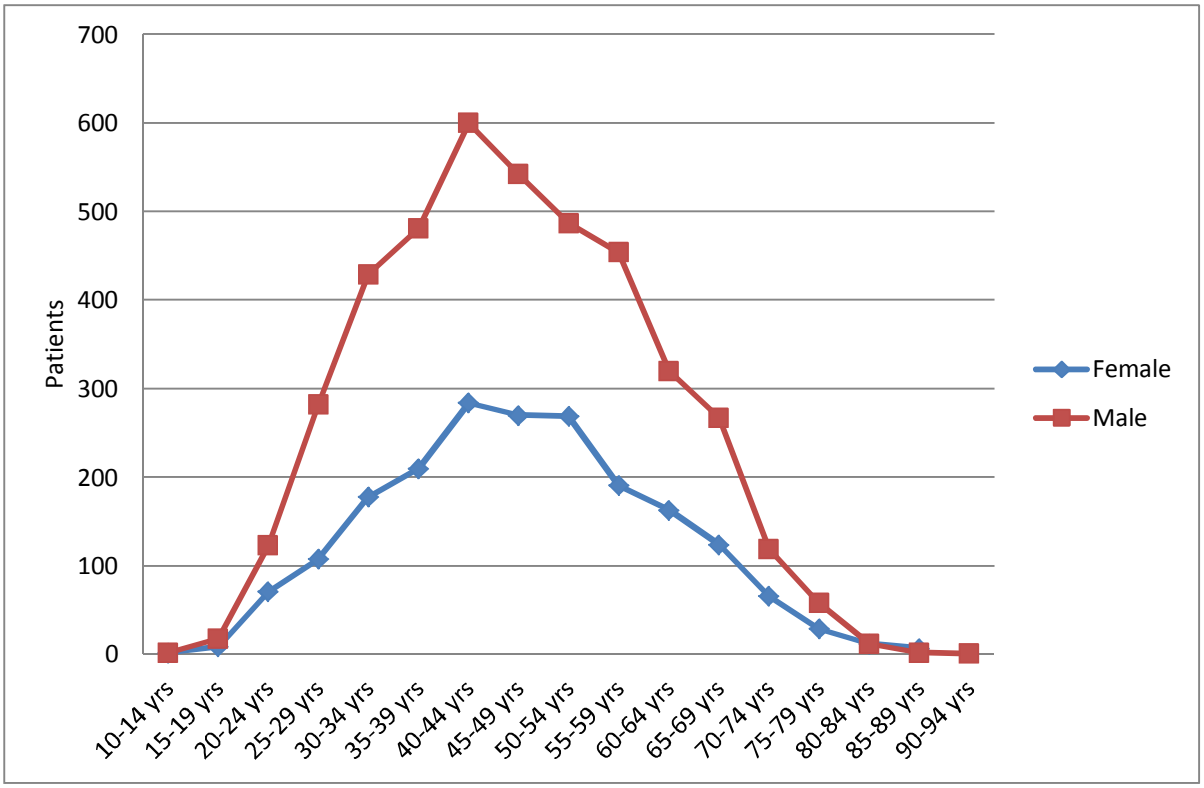


**Figure 5 –Patients on bDMARD therapy by age group and gender (supplied a bDMARD prescription in 2015Q3)**
Source: DHS Prescriptions Claims database, based on date of supply

Figure 5 shows that the most common age of patients receiving a supply in 2015 Q3 was 40-44 years. It also shows that the number of female patients (2,000) was less than half the number of males (4,207), a male to female prevalence ratio of 2.1.

Figure 6 shows the number of initiations to bDMARD therapy in the 12 months from 2014 Q4 to 2015 Q3. The number of males (721) is only slightly more than the number of females (632), a male to female incidence ratio of 1.1.

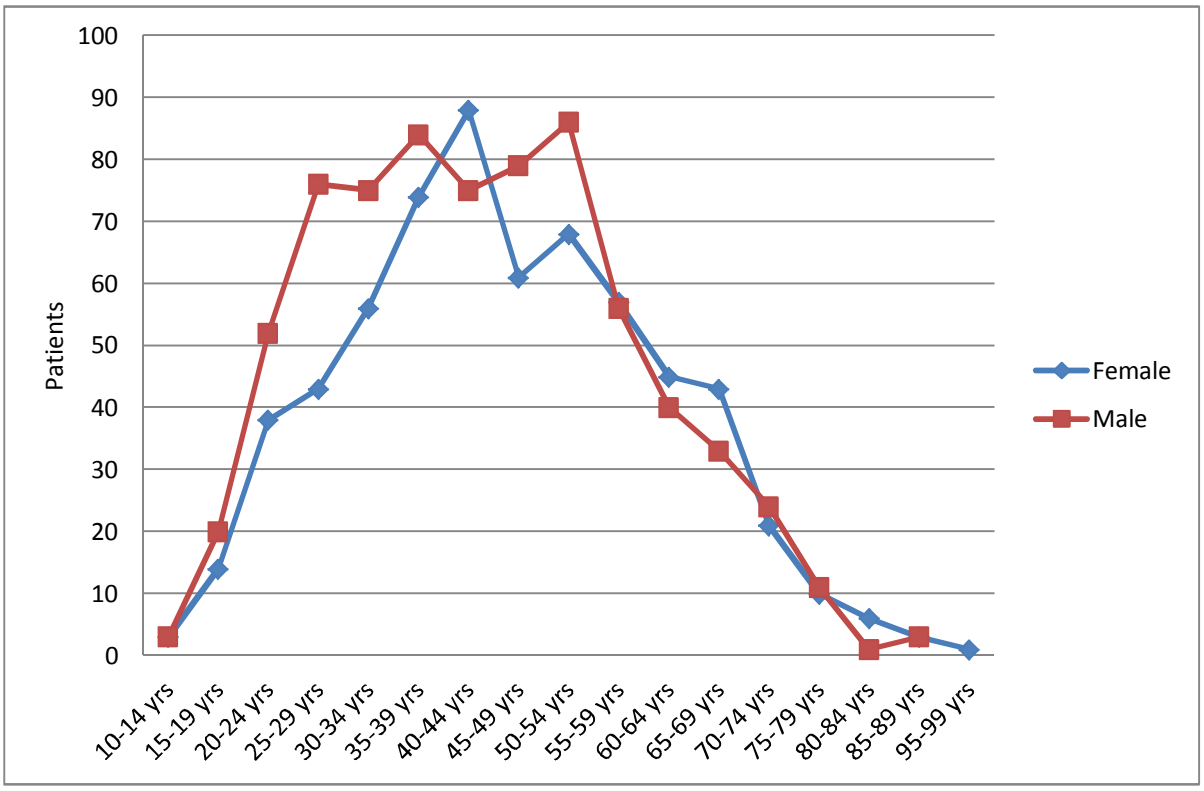


**Figure 6 –Patients initiating to bDMARD therapy by age group and gender in the 12 months from 2014 Q4 to 2015 Q3**

Source: DHS Prescriptions Claims database, based on date of supply

The reason for the difference in gender proportion between prevalent and initiating patients is not known but may be due to;

- the incidence of AS increasing for females relative to males over time; or
- the diagnosis and treatment rate increasing for females relative to males over time; or
- males continuing on treatment for longer than females.

At the time that bDMARDs were first available on the PBS it was understood that the prevalence of ankylosing spondylitis was higher in males than females. Although the condition is recognised as most frequently developing in young men, the male:female ratio has more recently been reported as 2-3:1[11]

[11] Brown M. Ankylosing spondylitis and the spondyloarthropathies. Australian Doctor. 27 February 2009 <http://www.australiandoctor.com.au/cmspages/getfile.aspx?guid=ddf8099c-41a4-4467-af84-4cbb8b24aaf5>

***Continuation***

Figure 7 presents the proportion of bDMARD therapy initiating patients who started treatment in 2012 by the number of approvals received. The 2012 calendar year cohort is presented to balance recent practice with an adequate period of follow-up data. A first authority approval generally provides sufficient therapy for 16 weeks (adalimumab, etanercept, golimumab) or 18 weeks (infliximab). Continuing authority approvals generally provide 24 weeks of treatment.

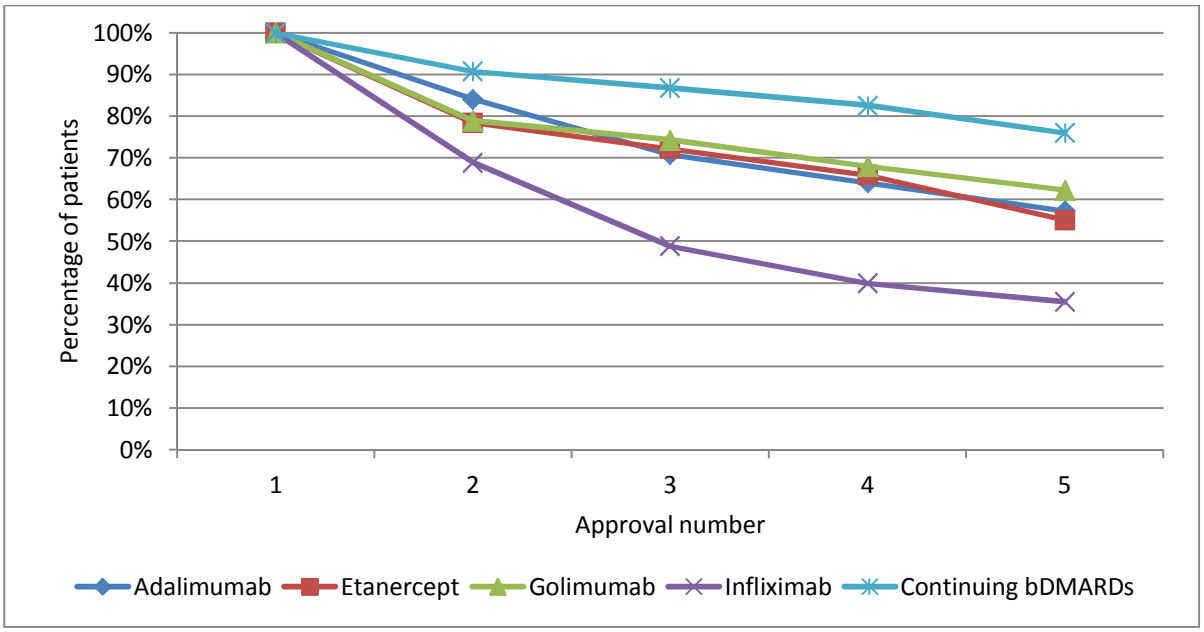


**Figure 7 - Continuation of bDMARDs for ankylosing spondylitis – patients initiating in 2012 (n=780)**

Source: DHS Authority Approvals database, approval date up until the end of October 2015

Note: Analysis truncated at fifth authority approval. Some patients receiving their first approval late in 2012 may not have sufficient time to receive a sixth approval by the end of the data period (ie. October 2015). Median time to the fifth approval was 93 weeks (ie. 1.8 years). This is an average of 23.3 weeks between approvals.

The rates of continuation are broadly similar across the three medicines administered subcutaneously (ie. adalimumab, etanercept or golimumab) with between 79% and 84% of patients receiving a second authority approval for their first prescribed bDMARD; and 55-62% receiving at least five authority approvals. Continuation with any bDMARD therapy is substantially higher than continuation with any individual medicine, with 91% of patients starting bDMARD therapy receiving a second authority approval for any drug and 76% with at least five authority approvals.

The lower rate for infliximab (69% receiving a second authority approval) may be related to the fact that it is an infusion that needs to be administered in a hospital or clinic. Switching to one of the other drugs, which are administered via a less burdensome subcutaneous injection, may explain the lower continuation rate on infliximab.

To consider continuation on treatment over a longer time period, Figure 8 presents the rate of continuation with bDMARD treatment for an earlier cohort of patients who started

treatment in 2009. At the time of data extraction, these patients had sufficient time to receive their tenth authority approval.

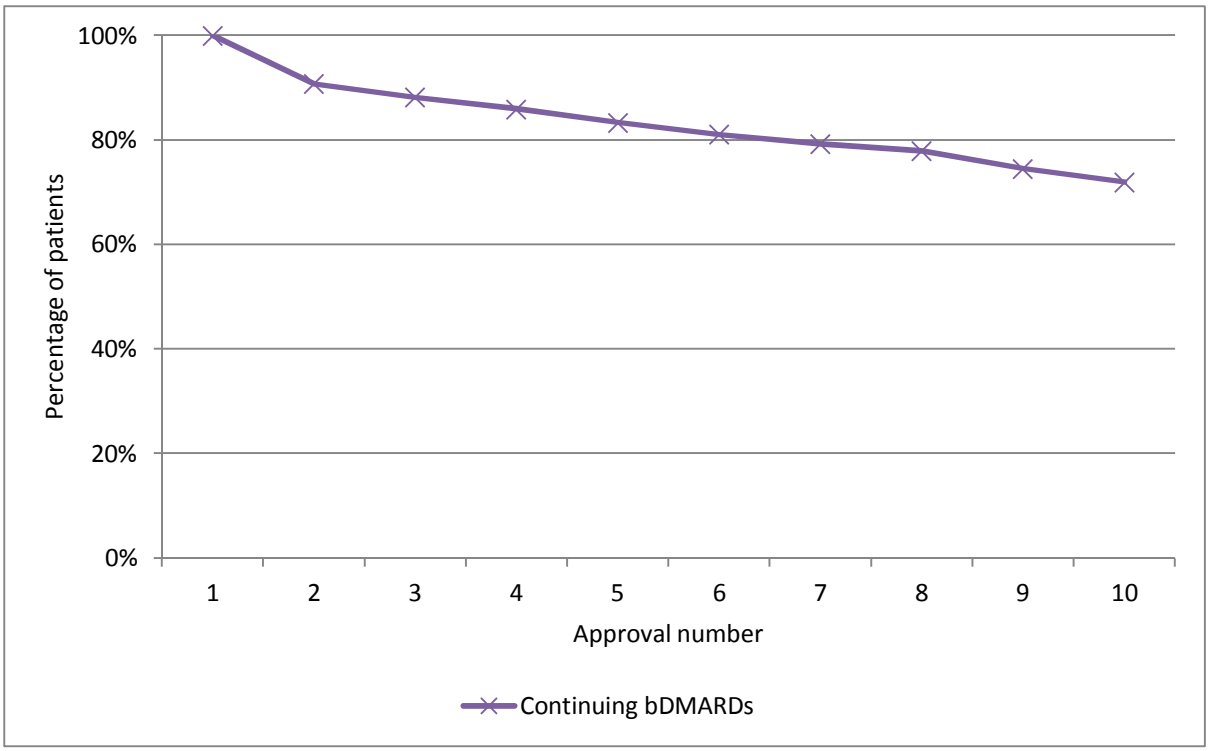


**Figure 8 - Continuation of bDMARDs of ankylosing spondylitis – patients initiating in 2009 (n=660)**

Source: DHS Authority Approvals database, approval date up until the end of October 2015
Note: Analysis is truncated at the 10th authority approval. Some patients receiving their first approval late in 2009 may not have sufficient time to receive an 11th approval by the end of the data period (ie. October 2015). Median time to the tenth approval was 221 weeks (ie. 4.3 years). This is an average of 24.6 weeks between approvals.

The majority of patients (72%) who started their first bDMARD for ankylosing spondylitis in 2009 received a tenth bDMARD authority approval.

***Number and Sequence of bDMARDs***

The sequence of bDMARDs for patients receiving their first authority approval before 1 January 2014 is shown in Table 3. As of November 2015, the majority of these patients (61.8%) remain on their first prescribed bDMARD, 26.7% and 9.2% have switched to a second or third bDMARD, respectively. Very few patients (2.2%) have progressed to a fourth or fifth agent.

**Table 3: Number of bDMARDs approved by initiating drug**

| | | Number of bDMARDs approved | | | | | |
|---|---|---|---|---|---|---|---|
| **Initiation drug** | | **1** | **2** | **3** | **4** | **5** | **Total** |
| **ADALIMUMAB** | patients | 1,701 | 666 | 240 | 47 | 4 | 2,658 |
| | % patients | 64.0% | 25.1% | 9.0% | 1.8% | 0.2% | 100.0% |
| **ETANERCEPT** | patients | 1,138 | 486 | 140 | 32 | 2 | 1,798 |
| | % patients | 63.3% | 27.0% | 7.8% | 1.8% | 0.1% | 100.0% |
| **GOLIMUMAB** | patients | 424 | 126 | 36 | 10 | 4 | 600 |
| | % patients | 70.7% | 21.0% | 6.0% | 1.7% | 0.7% | 100.0% |
| **INFLIXIMAB** | patients | 636 | 408 | 165 | 38 | 3 | 1,250 |
| | % patients | 50.9% | 32.6% | 13.2% | 3.0% | 0.2% | 100.0% |
| **Total** | patients | **3,899** | **1,686** | **581** | **127** | **13** | **6,306** |
| | % patients | **61.8%** | **26.7%** | **9.2%** | **2.0%** | **0.2%** | **100.0%** |

Table 3 shows that more patients who initiated on infliximab had more than 3 bDMARDs (i.e. 3% compared to approximately 2% for the other drugs); however the rate is still low.

Table 4 shows the top 20 bDMARD sequences.

**Table 4: Top 20 bDMARD sequences**

| bDMARD sequence | Patients | % Patients | Rank |
|---|---|---|---|
| ADALIMUMAB | 1701 | 27.0% | 1 |
| ETANERCEPT | 1138 | 18.0% | 2 |
| INFLIXIMAB | 636 | 10.1% | 3 |
| GOLIMUMAB | 424 | 6.7% | 4 |
| ETANERCEPT -> ADALIMUMAB | 343 | 5.4% | 5 |
| ADALIMUMAB -> ETANERCEPT | 316 | 5.0% | 6 |
| ADALIMUMAB -> GOLIMUMAB | 240 | 3.8% | 7 |
| INFLIXIMAB -> ADALIMUMAB | 189 | 3.0% | 8 |
| INFLIXIMAB -> ETANERCEPT | 175 | 2.8% | 9 |
| ADALIMUMAB -> INFLIXIMAB | 88 | 1.4% | 10 |
| ADALIMUMAB -> ETANERCEPT -> GOLIMUMAB | 88 | 1.4% | 11 |
| ETANERCEPT -> GOLIMUMAB | 73 | 1.2% | 12 |
| GOLIMUMAB -> ADALIMUMAB | 71 | 1.1% | 13 |
| INFLIXIMAB -> ETANERCEPT -> ADALIMUMAB | 65 | 1.0% | 14 |
| ETANERCEPT -> INFLIXIMAB | 64 | 1.0% | 15 |
| INFLIXIMAB -> ADALIMUMAB -> ETANERCEPT | 55 | 0.9% | 16 |
| ADALIMUMAB -> GOLIMUMAB -> ETANERCEPT | 43 | 0.7% | 17 |
| ETANERCEPT -> ADALIMUMAB -> GOLIMUMAB | 43 | 0.7% | 18 |
| ETANERCEPT -> ADALIMUMAB -> INFLIXIMAB | 43 | 0.7% | 19 |
| INFLIXIMAB -> GOLIMUMAB | 42 | 0.7% | 20 |
| Other | 469 | 7.4% | |
| Total | 6,306 | 100.0% | |

The two most common single switches were etanercept -> adalimumab (5.4%) and adalimumab -> etanercept (5.0%). The two most common double switches were adalimumab -> etanercept -> golimumab (1.4%) and infliximab -> etanercept -> adalimumab (1.0%). These patterns probably reflect the order and timing of the listing on the medicines on the PBS, as well as preference for subcutaneous administration.

***Analysis of expenditure***

The following table, Table 6, presents the total benefits paid for bDMARDs used for ankylosing spondylitis per year, based on date of supply.

**Table 6: bDMARD expenditure for ankylosing spondylitis**

| Listing years | 2004[a] | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Infliximab | $1,133,010 | $8,046,084 | $10,281,286 | $12,971,279 | $12,815,772 | $15,408,182 | $16,537,718 | $18,015,040 | $18,219,171 | $18,513,708 | $18,586,789 | $13,680,206 |
| Etanercept | | $3,765,042 | $8,407,847 | $12,583,346 | $18,381,295 | $21,305,350 | $19,964,885 | $20,708,944 | $23,149,373 | $25,080,226 | $26,448,083 | $20,624,502 |
| Adalimumab | | | | $3,225,894 | $11,404,122 | $18,153,863 | $23,027,515 | $26,436,753 | $30,865,842 | $35,874,030 | $42,999,153 | $35,613,977 |
| Golimumab | | | | | | | $1,443,276 | $7,173,522 | $10,482,606 | $14,566,338 | $19,037,294 | $16,432,512 |
| Certolizumab pegol | | | | | | | | | | | $374,916 | $2,421,815 |
| Ankylosing spondylitis total | **$1,133,010** | **$11,811,126** | **$18,689,133** | **$28,780,519** | **$42,601,189** | **$54,867,395** | **$60,973,394** | **$72,334,259** | **$82,716,993** | **$94,034,301** | **$107,446,234** | **$88,773,013** |

Source: DUSC Database and DUSC HSD database, extracted December 2015

[a] these data are for part of the year. The first bDMARD for ankylosing spondylitis was listed on 1 August 2004

[b] Data complete to 30 September 2015

Total expenditure on bDMARDs for ankylosing spondylitis has increased each year since listing, from approximately $1.1 million in 2004 (only infliximab) to $11.8 million in 2005 (etanercept listed 1 April 2005), to $61.0 million in 2010 (adalimumab listed 2007, golimumab listed 2010), and reached over $107 million in 2014.

## Discussion and Secretariat comments

The number of patients on bDMARD therapy for ankylosing spondylitis has increased from 628 in 2005 to 6,106 in 2014, and shows no indication of plateauing. A large majority of patients continue treatment with bDMARDs, whilst a majority of patients receiving subcutaneous bDMARDs (adalimumab, etanercept and golimumab) continue treatment on their first bDMARD for long periods (ie. at least 5 authority approvals).

The majority of patients (69-84%) who commenced bDMARD therapy in 2012 received a second authority approval for their first bDMARD, and 91% received a second authority approval for any bDMARD. Continuation rates in practice are generally higher than those observed in the clinical trials used as the basis for PBS listing.

***Trials Summary***

*Infliximab: P01522 was the primary trial used in the submission, and used a 50% improvement in BASDAI score (which most closely reflects the restriction) as the primary outcome. The pivotal trial reported at week 12 a response rate of 51.4%. (Source: Infliximab for AS submission, December 2003. Clinical trial results now published.)*

*Etanercept: Studies 016.0037 and 016.0626 used ASAS20* (Assessment in Ankylosing Spondylitis response with at least a 20% improvement) *at 12 weeks to measure response, with etanercept achieving a 60% and 65% response rate, respectively. (Source: Etanercept for AS Submission, July 2004. Clinical trial results now published.)*

*Adalimumab: the majority of trials used ASAS20 at 12 weeks compared to placebo, which reported significantly higher proportions of patients achieving ASAS20 for adalimumab. (Source: Adalimumab for AS Public Summary Document (PSD), November 2006). In clinical trials M03-606 and M03-607, adalimumab had a response rate (ASAS20) of 47.4% and 58.2%, respectively. (Source: Adalimumab for AS submission, November 2006. Clinical trial results now published.)*

*Golimumab: ASAS20 at 12, 14 or 24 weeks was the primary outcome for all trials. The proportion of patients achieving a 50% improvement in the Bath ankylosing spondylitis activity index (BASDAI) at Weeks 12/14 was the other outcome. No significant difference in ASAS20 outcome was observed between golimumab and any of infliximab, etanercept or adalimumab. In addition, no substantial differences in toxicity between golimumab and etanercept, adalimumab or infliximab, with the exception of injection site reactions, were found. (Source: Golimumab for AS PSD, March 2010)*

The percentage of patients receiving a second (ie. first continuing) authority approval corresponds to the percentage of patients who have responded (according to the restriction criteria) at approximately 16 weeks for adalimumab, etanercept and golimumab and approximately 18 weeks for infliximab. These continuation rates were 84%, 78%, 79% and 69% for adalimumab, etanercept, golimumab and infliximab respectively. These are substantially higher than the 12 week continuation rates in the Trials Summary above.

Sixty-two percent of patients who initiated bDMARD therapy for AS between 2004 and 2013 (inclusive) have remained on their first bDMARD thus far. For patients who do switch, the most common switches are between adalimumab and etanercept.

Only a small proportion of patients (2.2%) had more than the 3 bDMARDs. This may include switching between therapies without losing response and may not indicate they have completed a treatment cycle.

## DUSC consideration

The majority (69-84%) of patients who start a bDMARD receive a second authority approval for the same bDMARD, and 91% of patients receive a second authority approval for any bDMARD. Continuation rates in practice, assessed by the proportion of people who receive a second authority approval, are generally higher than response rates in the clinical trials used as the basis for PBS listing. The key trials indicated response rates of between 47-58% based on the ankylosing spondylitis assessment score 20% response (ASAS20) at 12 weeks. Higher continuation rates in practice than trial based continuation rates have been observed for bDMARDs used in other indications including rheumatoid arthritis (RA) and psoriasis. The DUSC has previously considered that there may be clinician or patient reluctance to withdraw a treatment where patients are achieving a partial response. DUSC considered that the high continuation rates for ankylosing spondylitis were related to there being few alternative therapies.

In their Pre-Sub-Committee Response (PSCR), a Sponsor claimed "it is inappropriate to compare the ASAS20 response rates in the pivotal clinical trials with PBS continuation rates as these outcomes are not comparable and therefore such a comparison is invalid and cannot be used as a basis to conclude that PBS continuation rates with the biologics are higher than those observed in the clinical trials". DUSC considered that the Sponsor makes some appropriate points about the lack of comparability of ASAS20 and PBS continuation criteria. DUSC recognised that while ASAS and the PBS criteria are not exactly the same, the ASAS is not more stringent.

More than half of patients initiating bDMARD therapy had remained on their first bDMARD at end of analysis (Table 3). For patients who switched to another therapy, the most common switches were between adalimumab and etanercept. DUSC considered that the number of patients moving to additional bDMARDs may increase in the future as there may be a loss of response to bDMARDs over time.

The DUSC also considered that:

- epidemiological data show that the ratio of male:female prevalent patients is around 3:1.This is the ratio assumed in the original infliximab submission to the December 2003 PBAC quoting the references, Arnett 1989[12] and Boyer et al. 1997[13]. The gender

[12] Arnett RC. Spondylarthropathies, in Textbook of Internal Medicine (Eds: Kelley WB, De Vita VT Jr, Du Pont HL). Philadelphia, PA: JB Lippincott; pp 986–990. 1989

comparison in the analysis shows a male:female ratio of approximately 2:1 for prevalent patients (Figure 5) and approximately 1:1 for initiating patients (Figure 6). DUSC considered that the reason for this inconsistency between the literature and the PBS data was unclear and warranted further investigation. DUSC suggested the Secretariat provide a time series of the male:female ratio for prevalent and initiating patients to see if the ratio has changed over time, and to review more recent epidemiological data. A concern was that the unexpected gender ratio may reflect leakage into treatment of other inflammatory conditions.

DUSC noted that in their PSCR, a Sponsor had considered the method of measuring continuation rates in the analysis to be inappropriate and to overestimate persistence. The sponsor claimed that the continuation rate was less if measured using prescription supply data rather than authority approval data. Authority approval data was used in the DUSC analysis due to lack of completeness of patient level prescription supply data (due to the fact that infliximab is part of the S100 HSD Schedule). This limitation is decreasing with time and the Secretariat will be able to use prescription supply data in future continuation analysis of bDMARDs. DUSC also noted the Authority approval data does reflect prescriber intent to continue therapy. The Sponsor used the DHS PBS 10% patient sample of prescription supply data and a different methodology to estimate an alternative continuation rate. DUSC emphasised that analyses using the PBS 10% patient sample need to be cognisant of the final sample size. For example, the DUSC analysis of long term continuation included all patients who initiated bDMARD treatment in 2009 (see Figure 8). There were 660 such patients, however an equivalent analysis in the PBS 10% patient sample would only have approximately 66 patients. Estimates based on this smaller sample size would have considerably broader 95% confidence intervals.

DUSC considered that methods to establish 'breaks in therapy' in utilisation reviews of bDMARDs need to be mindful that in clinical practice the frequency of bDMARDs administration may differ from that expected, for example less frequent dosing for patients who have achieved and are maintaining a response.

**Key Findings and Discussion**

DUSC considered that there are multiple reasons for high and increasing utilisation of bDMARDs for ankylosing spondylitis:

- There is no local epidemiological data on the incidence and prevalence of ankylosing spondylitis in Australia. DUSC considered that the population with ankylosing spondylitis may have been underestimated at the time bDMARDs were first listed for this indication. DUSC noted several more recent international epidemiological sources reporting higher prevalence of ankylosing spondylitis.
- Higher retention rates on bDMARD than predicted. DUSC considered that this may be partly driven by the restriction continuation rules. DUSC considered that there may be

[13] Boyer G S, Templin D W, Bowler A, Lawrence R C, Everett D F, Heyse S P, Cornoni-Huntley J, Goring W P. A comparison of patients with spondyloarthropathy seen in specialty clinics with those identified in a communitywide epidemiologic study. Has the classic case misled us? Archives of Internal Medicine 1997; (157): 2111-2117

clinician or patient reluctance to withdraw treatment where patients are achieving a partial response particularly as there is a lack of alternative therapies. In addition, there is no flexibility within the current restriction to suspend therapy or reduce therapy (if efficacious) and recommence at a later date.
- Treatment of earlier stage disease. DUSC considered that this may be clinically appropriate given the most recent data suggesting the efficacy of bDMARDs in slowing radiographic progression.
- Increased familiarity with bDMARDs, improved awareness of inflammatory back pain leading to more referrals from GPs to rheumatologists.

DUSC considered that the ratio of male:female bDMARD initiating and prevalent patients is inconsistent with known epidemiological data and requested further analysis of the PBS data and published literature.

## DUSC actions

The DUSC requested that:

- the report be provided to the PBAC; and
- the Secretariat produce a time series of the male:female ratio for prevalent and initiating patients to see if the ratio has changed over time.

## 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 agrees with the DUSC that there is now more epidemiological data and greater disease awareness regarding AS than there was at the time of listing. Any proposed changes to restriction wording should be checked with clinicians for clinical validity.

Pfizer Pty Ltd: The sponsor has no comment

Janssen-Cilag Pty Ltd: Janssen are committed to the appropriate and cost-effective use of its medicines, infliximab and golimumab, for the treatment of ankylosing spondylitis. Janssen believes that the written authority, with objective clinical requirements, ensures that the use of biologics remains within the PBS defined population". Further, the analyses conducted by the DUSC demonstrate that both golimumab and infliximab are being used within the PBS 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: Patients counts based on quarter of supply

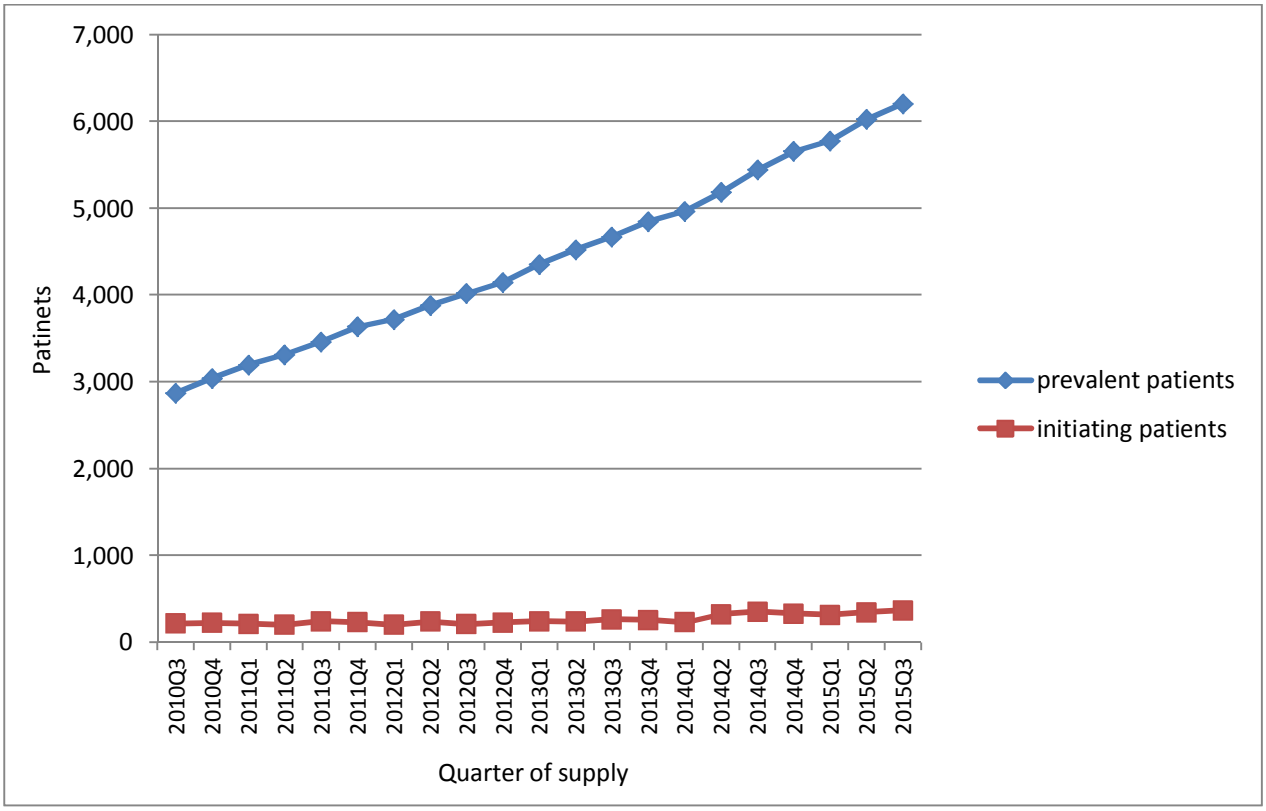


**Figure A.1: New and prevalent patients receiving bDMARD treatment by quarter**

Source: DHS Prescriptions Claims database, based on date of supply

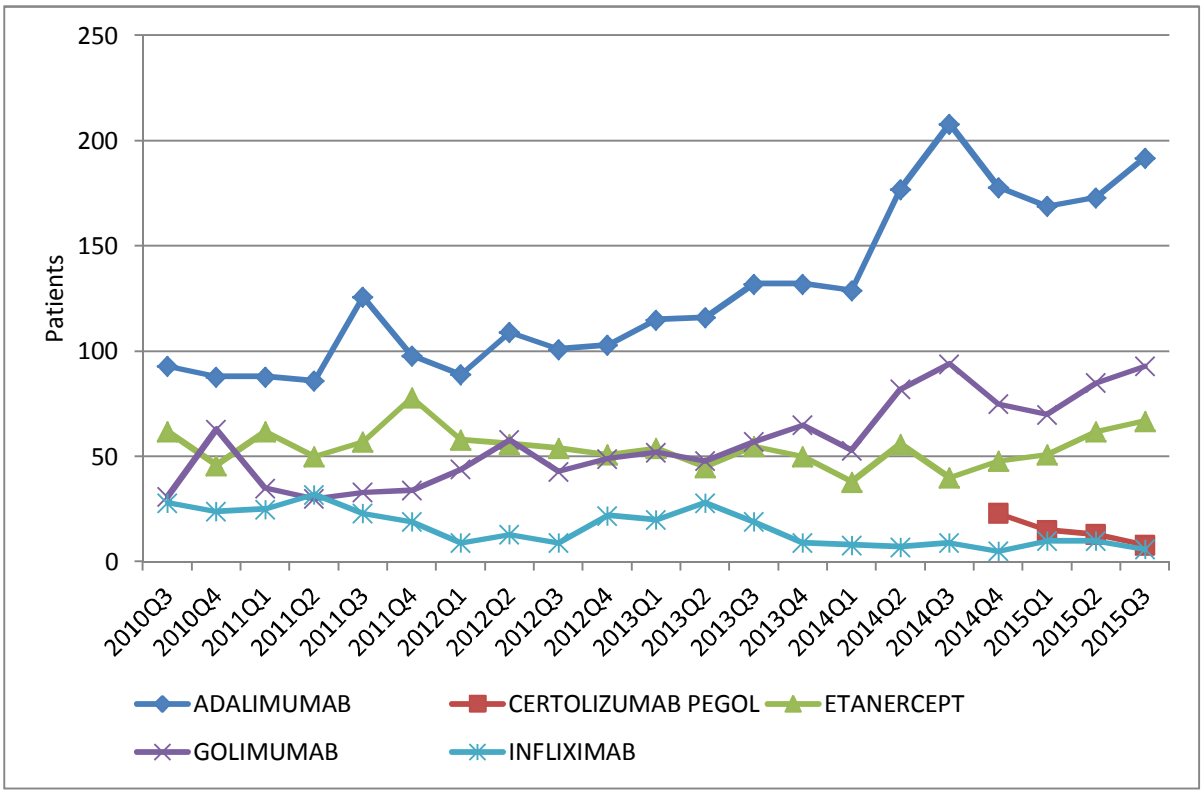


**Figure A.2: Patients initiating bDMARD therapy by initiating drug and quarter**

Source: DHS Prescriptions Claims database, based on date of supply

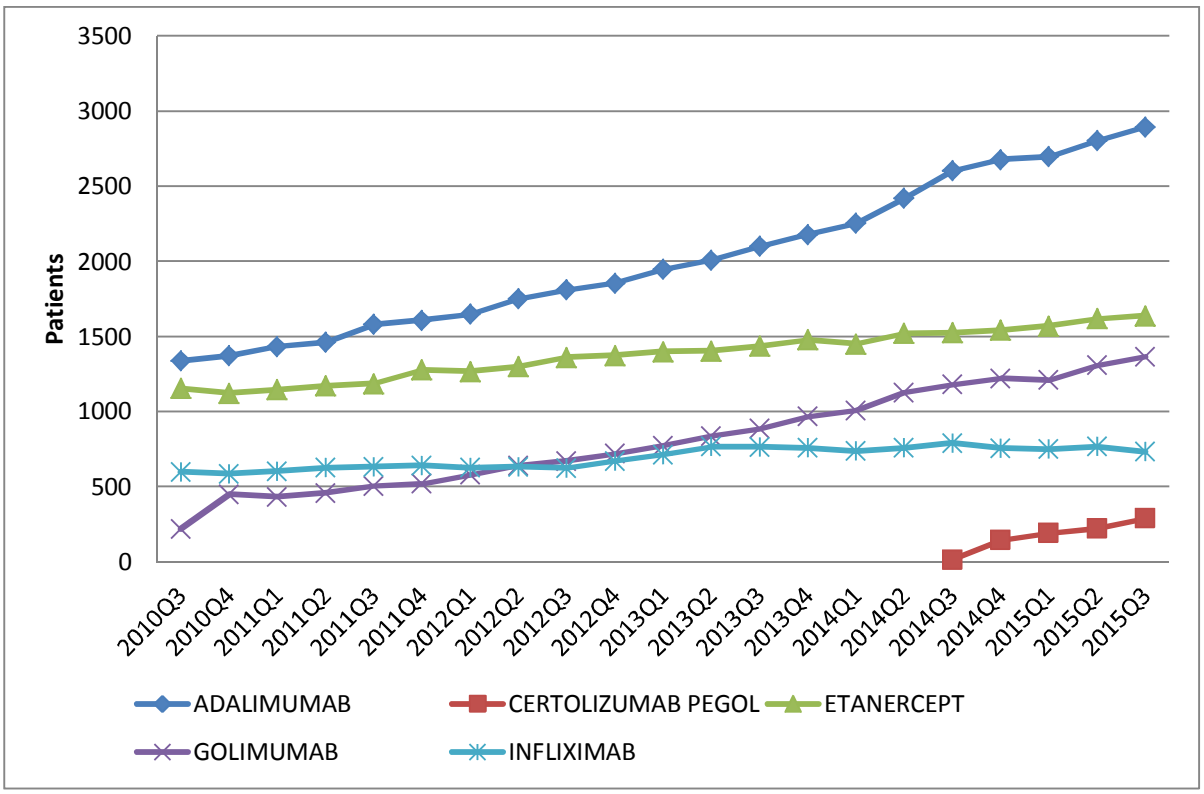


**Figure A.3: Prevalent patients by bDMARD and quarter of supply**

Source: DHS Prescriptions Claims database, based on date of supply