Crohn disease: infliximab, adalimumab and vedolizumab

Drug utilisation sub-committee (DUSC)

June 2017

Abstract

Note: By convention the term 'Crohn disease' rather than 'Crohn's disease' is used in the Pharmaceutical Benefits Schedule (PBS). The same convention is followed in this report.

Purpose

The PBAC considered the February 2015 DUSC review of biological disease modifying drugs (bDMDs) for Crohn disease at its March 2015 meeting. The PBAC noted that a higher than expected proportion of patients was continuing on bDMDs and their use to treat Crohn disease was yet to stabilise. The PBAC also noted that the cost-effectiveness of infliximab and adalimumab may be affected if patients are continuing treatment without achieving remission.

The PBAC requested for its DUSC to assess the utilisation of bDMDs for Crohn disease in another two years.

Listings on the Pharmaceutical Benefits Scheme (PBS)

Infliximab and vedolizumab are Section 100 Authority Required listings. Adalimumab has Authority Required General Schedule listings.

PBS first listing date	Drug	Listed indication
1 October 2007	Infliximab	Patient aged 6 to 17 years inclusive with moderate to severe refractory Crohn disease
1 October 2007	Infliximab	Severe refractory Crohn disease in adults
1 August 2008	Adalimumab	Severe refractory Crohn disease in adults
1 August 2010	Infliximab	Fistulising Crohn disease
1 April 2011	Adalimumab	Fistulising Crohn disease
1 August 2015	Infliximab	Moderate to severe Crohn disease
1 August 2015	Vedolizumab	Severe refractory Crohn disease
1 August 2015	Adalimumab	Patient aged 6 to 17 years inclusive with severe refractory Crohn disease

The restrictions are complex and patients must meet eligibility criteria regarding disease severity and have failed a prior course of corticosteroids and immunosuppressive therapy with azathioprine or 6-mercaptopurine or methotrexate, unless contraindicated, for non-

fistulising disease. Patients also need to achieve a defined response to continue on treatment.

Data Source / methodology

The Department of Human Services (DHS) Authority Approvals database was used for the analyses of continuation on bDMD treatment. The DHS Supplied Prescription database was used to analyse expenditure, derive incident and prevalent patient counts from 2014 to 2016 and to examine prior therapy received by a cohort of first time initiators on a bDMD in 2016. The DUSC Highly Specialised Drugs database was used to analyse the expenditure for infliximab prior to July 2013.

Key Findings

- The number of patients treated with bDMDs for severe refractory adult Crohn disease, fistulising Crohn disease and moderate to severe refractory Crohn disease in children and adolescents had increased steadily from 2007 to 2016.
- In 2016, 7,505 patients received a bDMD for severe adult refractory Crohn disease, 2,135 for fistulising Crohn disease and 824 patients received treatment for paediatric Crohn disease.
- The proportion of patients continuing on bDMD therapy for each of its listed Crohn indications was substantially higher than anticipated.
- bDMDs are being initiated as per their restrictions for prior therapies in the majority of cases.

Purpose of analysis

The PBAC considered the February 2015 DUSC review of biological disease modifying drugs (bDMDs) for Crohn disease at its March 2015 meeting. The PBAC noted that a higher than expected proportion of patients was continuing on bDMDs and their use to treat Crohn disease was yet to stabilise. The PBAC also noted that the cost-effectiveness of infliximab and adalimumab may be affected if patients are continuing treatment without achieving remission.

The PBAC requested its DUSC assess the utilisation of bDMDs for Crohn Disease in another two years.

Background

Clinical situation

Crohn disease is an inflammatory bowel disease (IBD) which can occur in any part of the digestive system. Ulcerative colitis is also a major type of IBD which is typically confined in the large intestine (GESA Guidelines, 2013). Between 5 to 15% of patients are estimated to have features of both conditions, referred to as 'IBD unclassified' (GESA Guidelines, 2013).

In Western countries, the age at diagnosis for IBD appears to be bimodal. An initial peak in diagnosis occurs between 20 to 30 years for Crohn disease and 30 to 40 years for ulcerative colitis. A second peak is seen in both diseases between 60 to 70 years of age (Ng et al., 2016). The predominance of a gender having IBD appears to vary depending on ethnicity and geographic region (Zelinkova and van der Woude, 2014). For instance, in Asian countries, Crohn disease is more prominent in males whereas in North America and Europe there seems to be an equal distribution to female predominance (Zelinkova and van der Woude, 2014).

The mechanisms underlying Crohn disease are complex and not fully understood. It is thought that the disease is the result of an abnormal immune response in the gut from either: an alteration in the balance of microorganisms (microbiota) in the intestinal tract; or environmental factors which disturb the mucosal layer within the bowel; or an immune response is triggered in an atypical way in genetically susceptible individuals (Guinane and Cotter, 2013; Boyapati et al., 2015). Environmental factors which are associated with a higher risk of developing Crohn disease include smoking, appendectomy and the use of antibiotics and nonsteroidal anti-inflammatory drugs (Ananthakrishnan 2013; Zelinkova and van der Woude, 2014; Ng et al., 2016).

Inflamed tissue within the bowel can become swollen and thick that can cause obstructions which may require surgery. Open sores (ulcers) may develop on the surface of the intestine. If ulcers break through the intestinal wall, fistulas (cavities) may develop forming abnormal connections in the intestine or between the intestine and other organs such as the skin and bladder. Fistulas may cause food to bypass the areas of the bowel which are important for absorption. Fistulas that result in the drainage of bowel contents to the skin

and other tissues can become infected and form an abscess which can become life threatening if untreated.

Common symptoms of Crohn disease include diarrhoea, abdominal pain, appetite loss, weight loss, fatigue and fever. There is no cure for Crohn disease. Treatment aims to alleviate symptoms, maintain disease remission and to prevent relapses.

Dosage and administration

Table 1: Dosage and administration of infliximab, adalimumab and vedolizumab for moderate to severe Crohn in adults and children and fistulising Crohn

Brand name and sponsor	Product	Dose and frequency of administration
Remicade®, Janssen-Cilag Pty Ltd Inflectra®, Pfizer Australia Pty Ltd	Infliximab	**Moderate to severe disease in children, adolescents and adults** Induction regimen: 5 mg/kg given as a single intravenous infusion at 0, 2 and 6 weeks. Maintenance regimen: After an induction course, 5 mg/kg every 8 weeks. For patients who have an incomplete response during maintenance treatment, consideration may be given to adjusting the dose up to 10 mg/kg. PBS subsidy is for the 5 mg/kg dose only. Paediatric Crohn patients with an adjusted dose of more than 5 mg/kg every 8 weeks may be at greater risk for adverse reactions. Continuing use in children and adolescents (6-17 years) who do not respond within 10 weeks of the initial infusion is not supported by available data. **Fistulising Crohn** Induction regimen: 5 mg/kg given as a single intravenous infusion at 0, 2 and 6 weeks. Infliximab should cease if there is no response after the initial three doses. Maintenance regimen: 5 mg/kg every 8 weeks. There are no efficacy and safety data on the use of infliximab for the treatment of refractory fistulising Crohn disease beyond 54 weeks.
Humira®, AbbVie Pty Ltd	Adalimumab	**Moderate to severe disease in adults** Induction regimen: On Day 0, initial dose of 160 mg either as four injections or two injections on Day 0 and two injections on Day 1. Second dose of 80 mg as two injections on Day 14. Maintenance regimen: 40 mg starting at Day 28 and continuing fortnightly. **Moderate to severe disease in children and adolescents aged 6 to 17 years** <u>For less than 40 kg bodyweight</u> Induction regimen (for both moderate and severe disease): Initial dose of 80 mg as two injections of 40 mg on Day 0. Second dose

Brand name and sponsor	Product	Dose and frequency of administration
		on Day 14 as one 40 mg injection or two 20 mg injections. Maintenance regimen: For moderate disease, 10 mg starting Day 28 and continuing fortnightly. For severe disease, 20 mg starting Day 28 and continuing fortnightly. For patients weighting 40 kg or more Induction regimen (for both moderate and severe disease): Initial dose on Day 0 of 160 mg as four injections of 40 mg or as two 40 mg injections on Day 0 and two 40 mg injections on Day 1. Second dose on Day 14 of 80 mg as two 40 mg injections. Maintenance regimen: For moderate disease, 20 mg starting Day 28 and continuing fortnightly. For severe disease, 40 mg starting Day 28 and continuing fortnightly.
Entyvio®, Takeda Pharmaceuticals Australia Pty Ltd	Vedolizumab	**Moderate to severe disease in adults patients** The recommended dose regimen is 300 mg administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. Patients should be reviewed within 6 to 8 weeks of completing the induction regimen, corresponding to 12-14 weeks after initiation of induction treatment. Continued treatment is not recommended for patients who have not shown a clinical response by Week 14. A clinical response is defined as greater than or equal to 70-point decrease in CDAI score from baseline.

Source: Product information from the Therapeutic Goods Administration.

Pharmacology

Infliximab and adalimumab are recombinant human immunoglobulin monoclonal antibodies that bind to tumour necrosis factor (TNF-α) and inhibit its inflammatory action.[1,2]

Vedolizumab is a humanised IgG1 monoclonal antibody that binds to the human α4β7 integrin.[3]

PBS listing details (as at April 2017)

The listings are summarised separately for the severe Crohn, Fistulising Crohn and paediatric Crohn indications in Appendix A.

Infliximab and vedolizumab are Section 100 Authority Required listings. Adalimumab has Authority Required General Schedule listings.

[1] Infliximab (Remicade®) Product Information. Available from the Australian Register of Therapeutic Goods. Accessed 24 March 2017.
[2] Adalimumab (Humira) Product Information. Available from the Australian Register of Therapeutic Goods. Accessed 24 March 2017.
[3] Vedolizumab (Entyvio) Product Information. Available from the Australian Register of Therapeutic Goods. Accessed 24 March 2017.

Restrictions

The bDMDs included in this review have complex restrictions. Abridged versions are presented here by indication. For full details of the current restrictions refer to the PBS website.

Severe refractory Crohn disease:

For initial treatment, patients must be 18 years or older who meet the following criteria:

- Must have a diagnosis of severe Crohn disease diagnosed by a gastroenterologist or a consultant physician (either internal or general medicine specialising in gastroenterology); and
- Must have either failed a prior course of steroids or have evidence of being intolerant or contraindicated to steroids; and
- Must have failed prior immunosuppressive therapy with azathioprine or 6-mercaptopurine or methotrexate; and
- Crohn Disease Activity Index (CDAI) score greater than or equal to 300 (or 220 if affected by extensive small intestine disease).

Patients may receive an initial authority approval for up to 16 weeks of adalimumab treatment or 14 weeks of infliximab treatment.

For infliximab a maximum quantity and number of repeats to provide for an initial course of consisting of 3 doses at 5 mg per kg body weight per dose to be administered at weeks 0, 2 and 6, will be authorised.

For vedolizumab, a maximum quantity and number of repeats to provide for an initial course of consisting of one vial of 300 mg per dose, with one dose to be administered at weeks 0, 2 and 6, will be authorised.

Patients need to be assessed for response after 12 weeks of adalimumab treatment or, for infliximab and vedolizumab, up to 12 weeks after the first dose.

To receiving continuing treatment a patient must demonstrate an adequate response defined as a CDAI score of no greater than 150. Other criteria apply if a patient is affected by extensive small intestine disease.

A maximum of 24 weeks of treatment can be authorised for each application for continuing treatment.

Patients switching between treatments receive the same initial treatment duration and assessment to response as new patients.

Fistulising Crohn disease:

Eligibility for initial treatment requires a confirmed diagnosis of Crohn disease by a gastroenterologist or consultant physician with an externally draining enterocutaneous or rectovaginal fistule.

A patient is eligible for continuing treatment if they demonstrate an adequate response following at least 12 weeks of treatment defined as:

- a reduction of ≥ 50% in the number of open draining fistulae from baseline; and/or
- a marked decrease in drainage from all fistula(e) from baseline and less induration and pain reported by the patient.

A maximum of 24 weeks of treatment can be authorised for each application for continuing treatment. Patients are allowed to switch between infliximab and adalimumab.

Paediatric Crohn disease:

There are separate restrictions for moderate to severe and severe disease.

Moderate to severe disease

For initial treatment a patient must be aged 6 to 17 years inclusive and meet the following criteria:

- Have a diagnosis of Crohn disease confirmed by a gastroenterologist, consultant physician, paediatrician or specialist paediatric gastroenterologist; and
- Must have failed to achieve a response to two of the three following therapies: a course of prednisolone or an equivalent steroid over a 6 week period; an 8 week course of enteral nutrition; or 3 or more months of immunosuppressive therapy with either azathioprine, 6-mercaptopurine or methotrexate; or
- Must be intolerant or contraindicated to each of prednisolone (or equivalent), azathioprine, 6-mercaptopurine and methotrexate; and
- Demonstrate having moderate to severe disease defined as a Paediatric Crohn Disease Activity Index (PCDAI) score ≥ 30.

A maximum quantity and number of repeats to provide for an initial course of this drug consisting of 3 doses at 5 mg per kg body weight per dose to be administered at weeks 0, 2 and 6, will be authorised.

A PCDAI assessment of the patient's response to this initial course of treatment must be made up to 12 weeks after the first dose (6 weeks following the third dose).

To be eligible for continuing treatment a patient must demonstrate an adequate response defined as a PCDAI score of at least 15 points compared to baseline and a total of PCDAI score of 30 points or less with the PCDAI assessment being no more than 1 month old at the time of application.

A maximum of 24 weeks of treatment can be authorised for each application for continuing treatment.

Severe disease

For initial treatment a patient must be aged 6 to 17 years inclusive and meet the following criteria:

- Have a diagnosis of Crohn disease confirmed by a gastroenterologist, consultant physician, paediatrician or specialist paediatric gastroenterologist; and
- Must have failed to achieve a response to two of the three following therapies: a course of prednisolone or an equivalent steroid over a 6 week period; an 8 week course of enteral nutrition; or 3 or more months of immunosuppressive therapy with either azathioprine, 6-mercaptopurine or methotrexate; or
- Must be intolerant or contraindicated to each of prednisolone (or equivalent), azathioprine, 6-mercaptopurine and methotrexate; and
- Demonstrate having severe disease defined as a Paediatric Crohn Disease Activity Index (PCDAI) score ≥ 40.

A PCDAI assessment of the patient's response to an initial course of treatment must be made following a minimum of 12 weeks therapy.

For continuing treatment a patient must demonstrate an adequate response defined as a PCDAI score of 40 points or less with the PCDAI assessment being no more than 1 month old at the time of application.

A maximum of 24 weeks of treatment can be authorised for each application for continuing treatment.

Patients can switch between infliximab and adalimumab.

Therapeutic Goods Administration (TGA) approved indications

Infliximab is indicated for the treatment of Crohn disease in adults and in children and adolescents (6-17 years inclusive), specifically:

- the treatment of moderate to severe Crohn disease, to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional therapies; and
- the treatment of refractory Fistulising Crohn disease, for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.

Adalimumab is indicated for the treatment of moderate to severe Crohn disease in patients aged 6 years and older who have had an inadequate response to conventional therapies or have lost response to or are intolerant to infliximab.

Vedolizumab is indicated for the treatment of adult patients with moderate to severe Crohn disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNF-alpha) antagonist.

Infliximab, adalimumab and vedolizumab are also indicated for the treatment of several inflammatory conditions which are summarised in the following table.

Summary of approved indications as at April 2017

Approved indication	Infliximab	Adalimumab	Vedolizumab
Moderate to severe Crohn disease in adults	X	X	X
Moderate to severe Crohn disease in children and adolescents (6 to 17 years)	X	X	
Refractory Fistulising Crohn Disease in adults	X	X	
Ankylosing Spondylitis	X	X	
Enthesitis-related arthritis in children		X	
Moderately to severely active polyarticular juvenile idiopathic arthritis		X	
Moderate to severe chronic plaque psoriasis in adult patients	X	X	
Moderate to severe chronic plaque psoriasis in children and adolescents from 4 years of age		X	
Moderate to severely active psoriatic arthritis in adult patients	X	X	
Moderate to severely active rheumatoid arthritis in adults	X	X	
Moderate to severe ulcerative colitis in adults	X	X	X
Moderate to severe ulcerative colitis in children and adolescents (aged 6 to 17 years inclusive)			
Moderate to severe hidradenitis suppurativa (acne inversa) in adult patients		X	
Non-infectious intermediate, posterior and pan-uveitis in adult patients		X	

Source: Australian Register of Therapeutic Goods

Clinical guidelines

A similar approach is used in drug therapy for Crohn disease and ulcerative colitis. The following description of the therapeutic approaches used in Australia is based on the GESA Guidelines 2013:

- Initial therapy aims to alleviate symptoms and promote healing of the mucosa to prevent disease flares and other complications such as the development of ulcers. Common options include: corticosteroids (e.g. prednisolone, prednisone, budesonide); immunosuppressant drugs (methotrexate, 6-mercaptopurine, azathioprine); aminosalicylates (5-ASA) given orally or rectally (e.g. sulfasalazine, mesalazine, olsalazine, balsalazide); antibiotics; and biological agents (e.g. infliximab, adalimumab, vedolizumab). Corticosteroids are mainly used to treat acute flare-ups and to achieve rapid symptom relief. They are not recommended for longer-term therapy as they are associated with significant side effects.
- For maintenance therapy, steroid free drugs which are commonly used for maintaining remission from Crohn disease and ulcerative colitis include:
  - Immunosuppressant therapy including thiopurines (azathioprine, 6-mercaptopurine); methotrexate; and calcineurin inhibitors (cyclosporin, tacrolimus). These options enable patients to withdraw from steroid therapy.

Calcineurin inhibitors are mainly used for severe episodes which do not respond to high dose intravenous steroids.

- biological therapy. To access PBS subsidised bDMDs for Crohn and ulcerative colitis patients must fail conventional therapy with steroids and an immunosuppressive drug unless they are intolerant to these drugs. The GESA guidelines (2013) state that bDMDs may also be used in: first-line or as early aggressive therapy in patients who are unable to take standard therapy; or as part of concomitant therapy with immunosuppression as a short course or episodic therapy, but the benefits of continuing concomitant treatment are unclear.

Date of first listing for the bDMDs by indication

PBS first listing date	Drug	Listed indication
1 October 2007	Infliximab	Patient aged 6 to 17 years inclusive with moderate to severe refractory Crohn disease
1 October 2007	Infliximab	Severe refractory Crohn disease in adults
1 August 2008	Adalimumab	Severe refractory Crohn disease in adults
1 August 2010	Infliximab	Fistulising Crohn disease
1 April 2011	Adalimumab	Fistulising Crohn disease
1 August 2015	Infliximab	Moderate to severe Crohn disease
1 August 2015	Vedolizumab	Severe refractory Crohn disease
1 August 2015	Adalimumab	Patient aged 6 to 17 years inclusive with severe refractory Crohn disease

Changes to listing

At the request of the Paediatric Medicines Advisory Group the corticosteroid dosing was changed for infliximab's listings for paediatric Crohn disease from a dose of 40mg daily to 1 mg per kg or 40 mg (whichever is lesser) from 1 January 2011.

A biosimilar for infliximab (Inflectra®) first listed from 1 December 2015.

Current PBS listing details are available from the PBS website.

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

Infliximab for Crohn disease was considered and not recommended by the PBAC in June 2000, December 2000 and September 2001.

******* Committee-in-confidence *******

[redacted]

******* End committee-in-confidence *******

March 2007 meeting – Infliximab for severe refractory Crohn disease

The PBAC recommended infliximab as a Section 100 (Highly Specialised Drug) Authority Required listing for patients with severe Crohn disease (Crohn Disease Activity Index greater than or equal to 300) or patient with a colectomy or ileostomy from Crohn disease on the basis of cost-effectiveness to placebo. The PBAC recommended that where a response to infliximab was not demonstrated, patients would not be eligible to recommence treatment with infliximab within 12 months of the date on which the treatment ceased.

For further details refer to the Public Summary Document from the March 2007 PBAC meeting.

May 2007 stakeholder meeting – listing criteria for infliximab

On 15 May 2007, a stakeholder meeting was held in relation to the listing criteria for infliximab for Crohn disease.

The PBAC, as part of its March 2007 recommendation, agreed to meet with clinicians to consider restriction criteria for patients in whom a CDAI was not appropriate. This included patients with ostomies, ileostomies and short bowel syndrome. For such patients other potential markers to measure disease activity were C-reactive protein, erythrocyte sedimentation rate, platelet count, lactoferrin or endoscopy.

It was agreed that the PBAC's recommendation to initiate infliximab based on a CDAI score of 300 was appropriate, with the exception of certain clinical circumstances.

An improvement in CDAI to less than 200 at 12 weeks was considered to be clinically appropriate as criteria for continuing therapy.

******* Committee-in-confidence *******

[redacted]

******* End committee-in-confidence *******

May 2007 special meeting – Infliximab for severe refractory Crohn disease

The PBAC considered a minor resubmission which sought to change the basis of the March 2007 recommendation in relation to the continuation criteria for infliximab for Crohn disease. For continuation beyond 12 weeks, the sponsor proposed that a patient achieve a 100-point reduction from their baseline CDAI. The PBAC had recommended the achievement of remission, defined as a CDAI of less than or equal to 150.

The PBAC considered the cost-effectiveness estimates presented in the resubmission served to heighten rather than allay these concerns.

The PBAC therefore deferred the submission and requested that the sponsor provide a new submission which addresses the concerns about the economic model and which provides cost-effectiveness estimates using the initiation and continuation criteria recommended by the participants at the stakeholder meeting. The PBAC reaffirmed its recommendation made in March to list infliximab for the treatment of severe Crohn disease with an initial CDAI of ≥ 300 and continuing treatment CDAI ≤ 150. The sponsor subsequently chose to proceed with the listing recommended at the March 2007 meeting.

July 2007 meeting – Infliximab for severe refractory Crohn disease in paediatric patients

Infliximab was recommended as a Section 100 (Highly Specialised Drug) Authority Required listing for patients aged 6 to 17 years inclusive with Crohn disease who are refractory to conventional therapy. The listing was recommended on the basis of an acceptable cost-effectiveness against placebo.

For further details refer to the Public Summary Document from the July 2007 PBAC meeting.

November 2007 meeting – Adalimumab for severe refractory Crohn disease

Adalimumab was recommended as a Section 100 (Highly Specialised Drug) Authority Required listing for moderate to severe Crohn disease (CDAI) > 300) or in patients with an ileostomy or colectomy due to Crohn disease on a cost-minimisation basis compared with infliximab.

It was agreed that the listing should be identical to infliximab, with the exception of use in the paediatric population as adalimumab had not been trialled in children.

For further details refer to the Public Summary Document from the November 2007 PBAC meeting.

March 2010 meeting – Infliximab for fistulising Crohn disease

Infliximab was recommended under Section 100 (Highly Specialised Drugs Program) Public and Private Hospital Authority Required for complex refractory fistulising Crohn disease with a draining enterocutaneous or rectovaginal fistula.

For the continuation criteria, the PBAC accepted that response could be assessed as either closure of at least 50 % in the number of externally draining fistulae (i.e. no drainage despite finger pressure in at least 50 % of fistulae) or a marked reduction in drainage of all fistulae together with less pain and induration as reported by the patient.

The PBAC did not agree to the request for two extra doses in the initiation phase as this was not consistent with the doses used in the trials or the TGA-approved dosing schedule.

For further details refer to the Public Summary Document from the March 2010 PBAC meeting.

November 2010 meeting – Adalimumab for fistulising Crohn disease

Adalimumab was recommended as an Authority Required benefit for the treatment of complex, refractory fistulising Crohn disease with a draining enterocutaneous or rectovaginal fistula on a cost-minimisation basis with infliximab.

The PBAC recommended that patients be permitted to cycle between PBS-subsidised infliximab and adalimumab using similar criteria to those for the severe refractory Crohn disease listings.

The PBAC noted that a proportion of patients with fistulising disease and a CDAI score ≥ 300 were already accessing PBS-subsidised adalimumab under the existing Crohn disease listing. The PBAC noted that there could be patients who were ineligible with worse fistulae but who have a lower CDAI. The PBAC considered that this represented an equity issue. The PBAC noted that the presence of fistulae adds only around 20 points to the overall CDAI score. The PBAC also noted that there was a high clinical need for alternative treatments that can be given by an alternative route other than intravenously.

April 2013 special meeting – Consideration of DUSC review of adalimumab and infliximab

The PBAC considered the DUSC predicted versus actual review of adalimumab and infliximab for fistulising Crohn at its April 2013 special meeting.

****** Committee-in-confidence ******

[redacted]

[redacted]

[redacted]

****** End committee-in-confidence ******

November 2014 meeting – Adalimumab for severe refractory Crohn disease in paediatric patients

The PBAC recommended extending the listing of adalimumab to include listing for the treatment of severe refractory Crohn disease in paediatric patients aged 6 to 17 years inclusive on a cost-minimisation basis with infliximab. The PBAC recommended an Authority required (written-only) restriction for both initial and continuing treatment.

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

March 2015 meeting – Vedolizumab for severe refractory Crohn disease

Vedolizumab was recommended as a Section 100 (Highly Specialised Drugs Program) Authority required listing for the treatment of severe Crohn disease in adult patients.

The recommendation was on a cost-minimisation basis with infliximab and adalimumab.

Consistent with the restrictions for infliximab and adalimumab, patients with short gut syndrome, an ostomy or extensive small intestine disease were included in the restriction for vedolizumab.

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

March 2015 meeting – Consideration of DUSC review of adalimumab and infliximab

In March 2015 the PBAC considered the February 2015 DUSC review on Crohn disease. The PBAC noted that the proportion of patients continuing treatment with infliximab or adalimumab was substantially higher than the rates of remission in the key clinical trials. The PBAC noted that that the CDAI, which is used to assess response and eligibility for continuing treatment for severe Crohn disease, has a number of subjective measures.

The PBAC noted that a higher than expected proportion of patients was continuing on bDMDs and their use to treat Crohn disease was yet to stabilise.

The PBAC also noted that the cost-effectiveness of infliximab and adalimumab may be affected if patients are continuing treatment without achieving remission. The PBAC considered that if a larger proportion of PBS patients are able to achieve remission due to

differences in clinical management or other factors, the use of these medicines may still be cost-effective.

The PBAC requested the DUSC assess the utilisation of bDMDs for Crohn disease in another two years.

For further details refer to the Consideration of the report of the Drug Utilisation Sub-committee from the March 2015 PBAC meeting.

July 2015 meeting – Recommendation of Inflectra as biosimilar of infliximab

The PBAC recommended the listing of infliximab (Inflectra®) as a biosimilar of infliximab (Remicade®) on a cost-minimisation basis to infliximab (Remicade®). The PBAC recommended that infliximab (Inflectra®) should have the same indications as infliximab (Remicade®).

For further details refer to the PBAC outcomes statement from the July 2015 PBAC meeting.

Previous reviews by the DUSC

The utilisation of bDMDs to treat severe Crohn disease was first reviewed by DUSC at its February 2011 meeting.

****** Committee-in-confidence ******

[redacted]

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[redacted]

****** End committee-in-confidence ******

At its February 2013 meeting the DUSC reviewed the utilisation of adalimumab and infliximab for fistulising Crohn disease. DUSC considered that the utilisation of adalimumab and infliximab for this indication was within the range expected for the first year of listing. DUSC noted that any future analyses of the utilisation of bDMDs for Crohn disease would be enhanced by assessing continuation and discontinuation rates. For further information of the DUSC consideration, refer to the outcome statement for the February 2013 DUSC meeting.

A further review of the use of adalimumab and infliximab in adult and paediatric patients with severe refractory Crohn disease and fistulising Crohn disease was considered by DUSC in February 2015. As seen in previous reviews, for each indication a higher proportion of patients continued on anti-TNF therapy than expected. DUSC noted the lack of Australian prevalence data to inform the original utilisation forecasts. The number of new paediatric patients treated with infliximab was higher than predicted. DUSC considered that this may have related to the change to the restrictions effective 1 January 2011 of the corticosteroid dosing requirements from 40 mg prednisolone equivalent to 1 mg/kg prednisolone or equivalent. For more details of the DUSC consideration, refer to the Public Release Document for the February 2015 DUSC meeting.

Methods

From 1 July 2013 there was complete prescription data capture for Highly Specialised Drugs (HSD) prescriptions dispensed by public and private hospital pharmacies. Prior to 1 July 2013, most HSD prescriptions supplied through public hospitals were processed

through the DHS Offline processing system, for which only aggregated data was available, i.e. the number of packs supplied and the cost per quarter. Infliximab first listed from 1 October 2007 as an s100 listing and its use is not fully captured in the DHS prescriptions data prior to July 2013. Therefore, to compare the findings from this analysis with the previous 2015 DUSC review of Crohn disease, patient level analyses including the number of incident and prevalent patients and drug continuations for infliximab, adalimumab and vedolizumab were undertaken using the DHS authority approvals data.

The number of packs and cost of infliximab before July 2013 was obtained from the DUSC Highly Specialised Drugs database. This source combines public hospital offline processed prescription data with public and private Hospital online processed prescription data with full capture of HSD drug utilisation.

Patient numbers

The DHS Authority approvals data was used to derive the number of incident and prevalent patients receiving an application to access bDMD therapy for Crohn disease.

The number of incident and prevalent patients treated with a bDMD in 2014, 2015 and 2016 was also derived from the DHS Prescriptions data as the HSD data was complete from July 2013.

The number of prevalent patients based on the Authorities or prescriptions data was determined by counting the number of people with an approval for at least one Authority application, or supply of a bDMD, using person specific numbers (non-identifying) in the data for the specified time periods, respectively. Patient initiation based on the Authorities or prescriptions data was defined as the date of Authority approval of the first application for a bDMD, or the date of the first supply of a bDMD, respectively.

Continuation on treatment

The DHS Authority approvals data was used to examine the continuation of infliximab, adalimumab and vedolizumab for their listed Crohn indications. The use of Authority approvals may overestimate continuation if a patient does not have a prescription dispensed or does not have the number of repeats dispensed as per the original prescription. However, any overestimate is likely to be small.

Same day authority approvals were counted as a single approval for the analysis of continuation. These were generally approvals for different strengths of the same drug.

A cohort of patients who were issued their first approval for a bDMD in 2011 for each indication was obtained. This was to update the continuation analyses done for the 2015 DUSC review of Crohn disease. The number of approved Authorities was counted for each patient up to December 2016. The number of Authority approvals was truncated to 11 as this was the maximum expected amount that a patient would receive when first initiating in 2011.

The continuation on bDMD therapy was also examined for cohorts of patients initiating in 2014 for each indication. The number of approved Authorities was counted for each patient

up to December 2016. The number of Authority approvals was truncated to 4 as this was the maximum expected amount that a patient would receive when first initiating in 2014.

Vedolizumab was first listed from 1 August 2015. Continuation on vedolizumab was examined in a six month cohort of patients who received their initial approval for this drug between August 2015 to January 2016. The number of approved Authorities was counted for each patient up to a maximum of three Authority approvals. This was the maximum expected amount of Authority approvals that a patient within the six month initiating cohort would receive.

Prior therapy

All supply records for the bDMD listings for each Crohn disease indication and for prior therapy in their restrictions, including prednisone, prednisolone, azathioprine, mercaptopurine and methotrexate, were extracted from the DHS Prescriptions database from January 2005 to December 2016.

Cohorts of patients first initiating on a bDMD for severe adult refractory Crohn disease, fistulising Crohn disease or paediatric Crohn disease in 2016 were obtained. The patient identifier for the initiating cohorts was used to identify the prior supply of a corticosteroid (prednisone, prednisolone) or immunosuppressive therapy (azathioprine, mercaptopurine or methotrexate).

Number of packs, prescriptions and expenditure

As noted above, the number of packs and expenditure for infliximab prior to July 2013 was extracted from the DUSC HSD database. For adalimumab, vedolizumab and infliximab post July 2013, the DHS Prescriptions database was used to obtain the prescriptions and expenditure data. As this analysis used the date of supply prescription data, there may be small differences compared with publicly available DHS Medicare date of processing data.[4] The publicly available DHS Medicare data only includes subsidised Repatriation PBS and PBS (R/PBS) prescriptions with prescriptions under the patient co-payment not included. The DHS Medicare data used in this report included under co-payment prescriptions from 1 April 2012.

[4] 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

Patient numbers

To allow a comparison to the 2015 DUSC review on Crohn disease, incident and prevalent patient counts are presented based on Authority approval data.

The annual number of incident and prevalent patients treated between 2014 and 2016, derived from the DHS Prescriptions data, are also presented.

Adult severe refractory Crohn disease

The number of prevalent patients supplied a bDMD for adult severe refractory Crohn disease had steadily increased from 2007 to 2016 (Figure 1). The number of patients treated with a bDMD had increased on average by 15% per year from 2013. The number of incident patients was relatively stable from 2009 to 2014 but increased in 2015 and 2016 (Figure 1). Some of the increase in the number of initiators from 2015 may relate to:

- the higher number of initiations seen in the paediatric patients from 2013 (Figure 3) who subsequently initiate on an adult bDMD listing. Of the initiators to an adult bDMD listing for severe Crohn disease in 2015 and 2016, 15% and 10% respectively had previously received a supply for a paediatric bDMD listing; and
- a modest number of patients in the long term extension study of vedolizumab (C13008) being 'grandfathered' after PBS listing on 1 August 2015 (Public Summary Document, vedolizumab, March 2015).

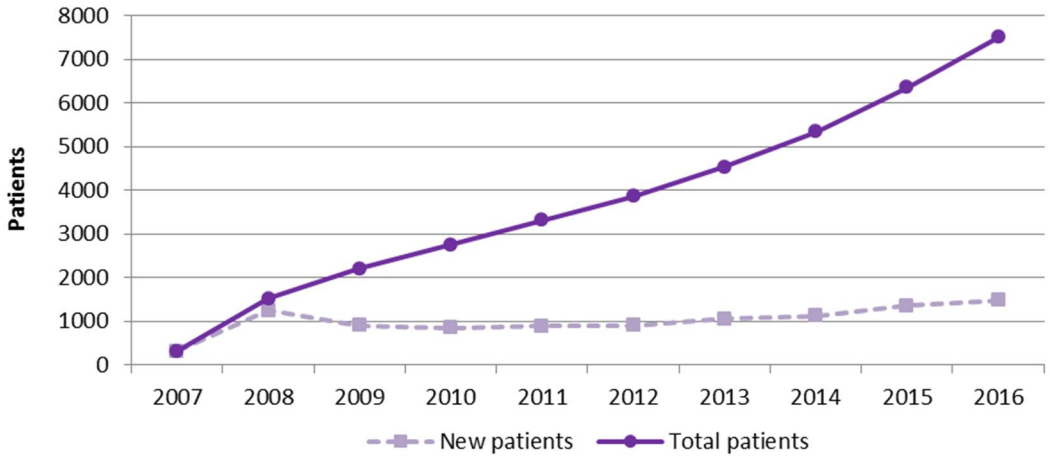

Figure 1: Number of patients receiving an Authority approval for severe adult refractory Crohn disease
Source: DHS Authority approvals database, accessed April 2017.

Table 2: Number of patients supplied a bDMD for severe adult refractory Crohn disease in 2014, 2015 and 2016

	2014	2015	2016
All bDMD drugs			
Incident[1]	1,049	1,236	1,373
Prevalent	5,323	6,332	7,505
By drug:			
Adalimumab			
Incident[1]	620	749	736
Prevalent	3232	3739	4173
Infliximab			
Incident[1]	429	462	522
Prevalent	2303	2730	3117
Vedolizumab[2]			
Incident[1]	-	25	114
Prevalent	-	25	138

Source: DHS Prescriptions database accessed April 2017.
[1] Incident patient counts are for the first ever episode of R/PBS treatment.
[2] 2015 has part year figures. Vedolizumab first listed on 1 August 2015.

Fistulising Crohn disease

The number of patients treated with a bDMD for fistulising Crohn disease had increased on average by 20% per year from 2013. The number of incident patients had remained relatively stable for this indication at around 450 patients per year since 2014.

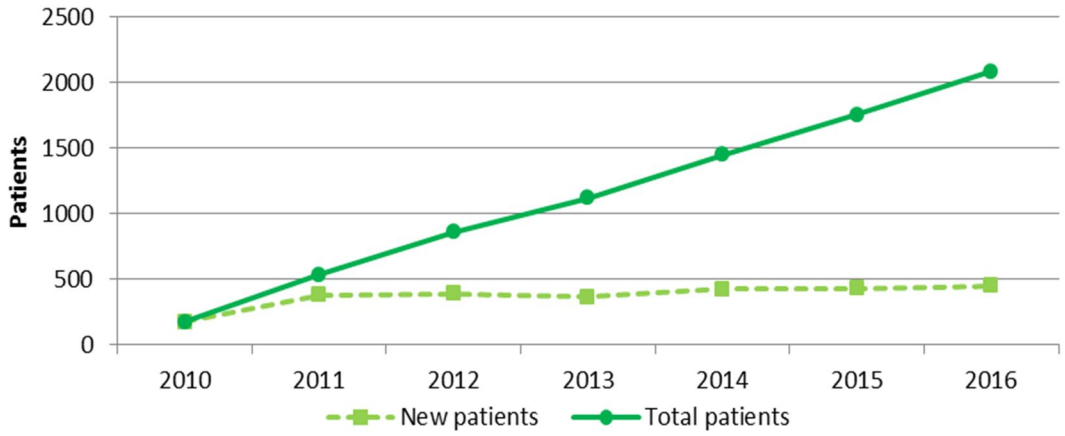

Figure 2: Number of patients receiving an Authority approval for Fistulising Crohn disease
Source: DHS Authority approvals database, accessed April 2017.

Table 3: Number of patients supplied a bDMD for fistulising Crohn disease in 2014, 2015 and 2016

	2014	2015	2016
All bDMD drugs			
Incident[1]	414	459	393
Prevalent	1,494	1,845	2,135
By drug:			
Adalimumab			
Incident[1]	215	232	179
Prevalent	746	940	1,048
Infliximab			
Incident[1]	199	227	213
Prevalent	804	963	1,165

Source: DHS Prescriptions database accessed April 2017.
[1] Incident patient counts are for the first ever episode of R/PBS treatment.

Paediatric Crohn disease

From 1 January 2011 the dosing of corticosteroids for infliximab's listings for paediatric Crohn disease changed from a dose of 40 mg daily to 1 mg per kg or 40 mg (whichever is lesser). This amendment may be associated with the rise in the number of new patients accessing a bDMD for this indication from 2012 (Figure 3).

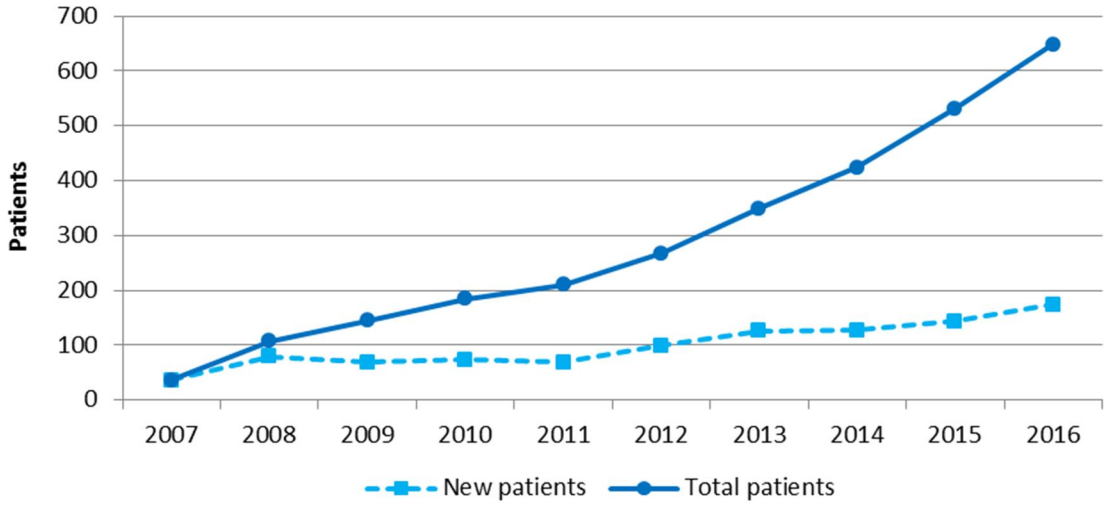

Figure 3: Number of patients receiving an Authority approval for paediatric Crohn disease
Source: DHS Authority approvals database, accessed April 2017.

Table 4: Number of patients supplied a bDMD for paediatric Crohn disease in 2014, 2015 and 2016

	2014	2015	2016
All bDMD drugs			
Incident[1]	122	185	331
Prevalent	427	588	824
By drug:			
Adalimumab[2]			
Incident[1]	-	67	214
Prevalent	-	67	250
Infliximab			
Incident[1]	122	118	117
Prevalent	427	521	577

Source: DHS Prescriptions database accessed April 2017.
[1] Incident patient counts are for the first ever episode of R/PBS treatment.
[2] 2015 has part year figures. Adalimumab first listed for the treatment of paediatric Crohn disease on 1 August 2015.

Continuation on bDMD therapy

The 2015 DUSC review on Crohn disease examined continuation on bDMDs for patients who first initiated in 2011. The continuation analyses for these 2011 initiating cohorts were extended to December 2016. This report also investigated the continuation rates for patients first initiating a bDMD in 2014 to compare whether the trend in continuation rates in a later patient cohort are different to the 2011 initiating cohort.

Figures 4 to 7 present the longer term rates of continuation for severe refractory Crohn disease in adults, fistulising Crohn disease and paediatric Crohn disease, respectively, in 2011. These figures show the rate of continuation with each drug separately as well as patients continuing treatment after switching from the initiating drug to an alternative bDMD.

Adult severe refractory Crohn disease

Of the adult patients with severe refractory Crohn disease initiating in 2011 who started bDMD therapy, around 60% remained on treatment after five years (Figure 4). The continuation rates for adalimumab were higher than infliximab for most of the analysis period, however after 11 approvals (approximately 5 years) the continuation rates were similar for adalimumab and infliximab (Figure 4).

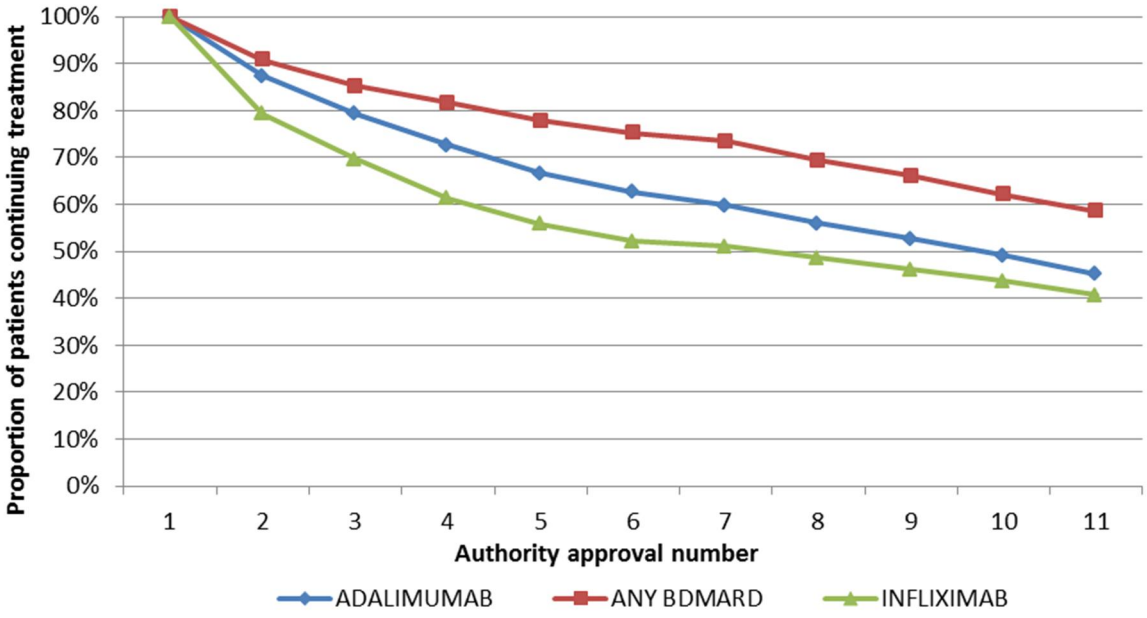

Figure 4: Continuation of bDMD treatment for severe Crohn disease – 2011 patients
Source: DHS Authority approvals database, accessed April 2017. Follow up to December 2016. "ANY BDMARD" refers to patients who switched from their initiating bDMD therapy to either adalimumab or infliximab.

At the time of reporting, only a limited amount of data was available for vedolizumab which first listed in August 2015 for severe refractory adult Crohn disease. A preliminary analysis of a six month cohort of patients receiving an initial Authority for vedolizumab between August 2015 and January 2016 was undertaken. This indicated that the continuation on vedolizumab was similar to the alternative intravenously administered bDMD, infliximab, which has the same frequency of administration, for up to three Authority approvals.

Fistulising Crohn disease

For patients first initiating on a bDMD for Crohn disease in 2011, the continuation rates were similar for adalimumab and infliximab over a five year period (Figure 5).

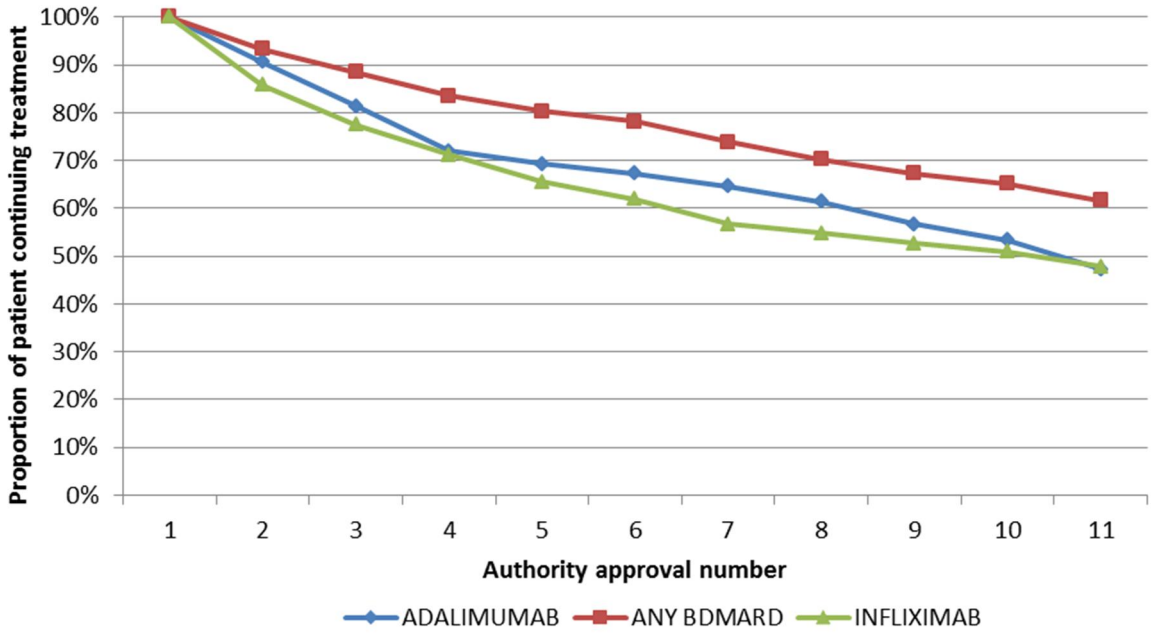

Figure 5: Continuation of bDMD treatment for fistulising Crohn disease – 2011 patients
Source: DHS Authority approvals database, accessed April 2017. Follow up to December 2016. "ANY BDMARD" refers to any bDMD.

Paediatric Crohn disease

Continuation on bDMDs was examined for patients initiating on the paediatric listings for moderate to severe Crohn disease in 2011 with a follow up to 31 December 2016. There were 50 patients who received a first supply of a bDMD in 2011. The mean age at initiation for the first supply was 14 years with a minimum age of 6 years and maximum age of 19 years. Of the 50 initiating patients, around half (54%) were aged 16 years or more. As such, a progressive decline in the continuation rate was expected as patients discontinue from no longer meeting the age criteria for the paediatric listings and move to the adult bDMD listings. After five years of therapy, corresponding to between 10 to 11 approvals for the typical patient, around 50% of patients received an approval for continuing bDMD therapy (Figure 6).

Adalimumab was listed for severe refractory Crohn disease in children and adolescents from August 2015. Of the 69 initiators in 2011, 18 patients had their Authority approval switched from infliximab to adalimumab.

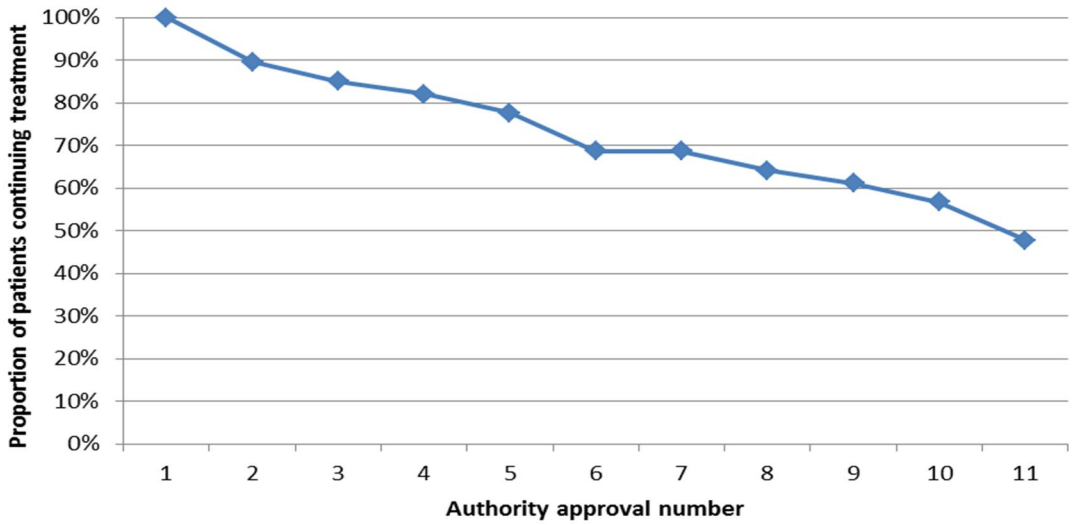

Figure 6: Continuation of bDMD treatment for moderate to severe paediatric Crohn disease – 2011 patients
Source: DHS Authority approvals database, accessed April 2017. Follow up to December 2016.

Comparison of continuation rates to any bDMD therapy between initiating cohorts in 2011 vs. 2014

For first initiators on a bDMD in 2014, complete data was available for the first four Authority approvals. Figure 8 compares the continuation rates between patient cohorts initiating in 2011 versus 2014 for each R/PBS Crohn indication. For each indication, the continuation rates were broadly similar for each initiating cohort (Figure 7).

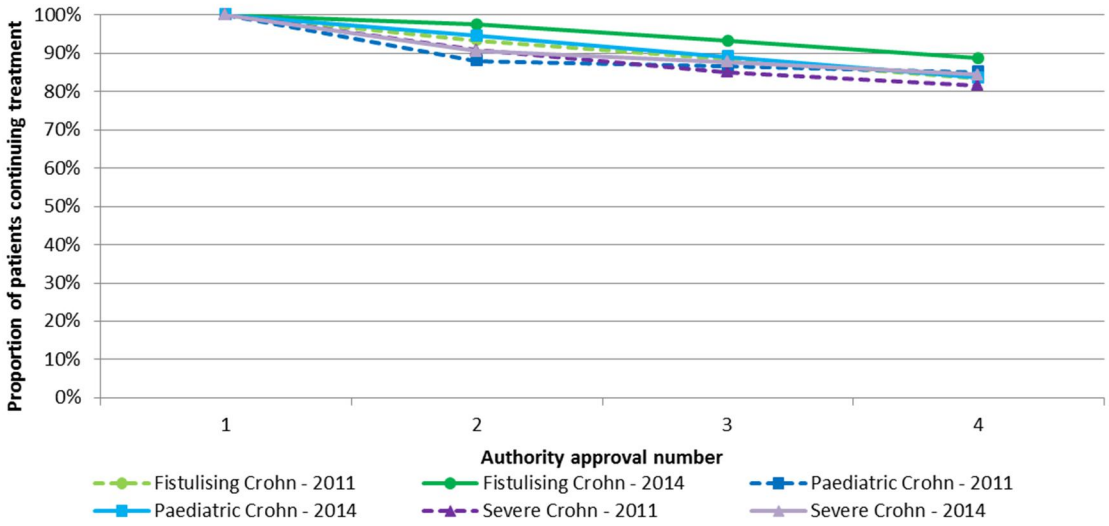

Figure 7: Comparison of continuation rates over the first four Authority approvals by indication for patients initiating a bDMD in 2011 vs. 2014
Source: DHS Authority approvals database, accessed April 2017.

Analysis of prior therapy before a bDMD

The PBS restrictions for bDMDs for adult severe refractory Crohn disease require that patients must have either failed a prior course of steroids or have evidence of being intolerant or contraindicated to steroids. The bDMD restrictions for paediatric Crohn disease require that patients must have failed to achieve a response to two of the three following therapies: a course of prednisolone or an equivalent steroid over a 6 week period; an 8 week course of enteral nutrition; or 3 or more months of immunosuppressive therapy with either azathioprine, 6-mercaptopurine or methotrexate; or patients must be intolerant or contraindicated to each of prednisolone (or equivalent), azathioprine, 6-mercaptopurine and methotrexate.

The use of corticosteroid and immunosuppressive therapy (azathioprine, 6-mercaptopurine or methotrexate) prior to a bDMD was examined for patients first initiating on a bDMD for severe refractory adult Crohn or paediatric Crohn disease in 2016. When interpreting the findings, it should be noted that there is only complete capture of undercopayment prescriptions from April 2012. As such, the use of some prior therapy before this time may not be detected in the analysis.

Adult severe refractory Crohn disease

Only a low proportion of patients first supplied a bDMD in 2016 for adult severe refractory Crohn disease did not receive a prior R/PBS supply of a corticosteroid or immunosuppressive therapy with azathioprine, 6-mercaptopurine or methotrexate (Table 5).

Table 5: Prior therapy supplied to patients with adult refractory Crohn disease who first initiated on a bDMD in 2016

	Patients	Proportion
Got a corticosteroid and immunosuppressive drug	1,183	86.2%
Got a corticosteroid only	35	2.5%
Got an immunosuppressive drug only	138	10.1%
No prior corticosteroid or immunosuppressive drug	17	1.2%
Total	**1,373**	**100.0%**

Source: DHS prescriptions database. Accessed on 13 April 2017.

Paediatric Crohn disease

A low proportion of patients first supplied a bDMD for moderate to severe paediatric Crohn disease in 2016 did not have a prior R/PBS supply of a corticosteroid or immunosuppressive therapy (Table 6).

Table 6: Prior therapy supplied to patients with paediatric Crohn disease who first initiated on a bDMD in 2016

	Patients	Proportion
Got a corticosteroid and immunosuppressive drug	240	72.5%
Got a corticosteroid only	19	5.7%
Got an immunosuppressive drug only	56	16.9%
No prior corticosteroid or immunosuppressive drug	16	4.8%
Total	**331**	**100.0%**

Source: DHS prescriptions database. Accessed on 13 April 2017.

Patients on adalimumab switching indications from severe adult to the paediatric listing

Before the listing of adalimumab for severe refractory Crohn disease in children and adolescents from August 2015, only a small number of patients less than 18 years of age were supplied adalimumab under the adult severe refractory Crohn disease listing. Between 2008 to 2016, the annual number of patients less than 18 years of age supplied adalimumab through its adult severe refractory Crohn listing ranged from 4 to 23.

Following adalimumab's listing for paediatric Crohn disease in August 2015, a small proportion of patients switched from the adult Crohn listing to the paediatric listing (Table 7). Of these, only 26% and 16% in years 2015 and 2016 respectively were less than 18 years of age. This suggests that the change in indication was mostly from an incorrect entry of the PBS item code rather than from children and adolescents transitioning to the paediatric listing when it became available.

Table 7: Proportion of patients supplied adalimumab who switched from the severe adult listing to the paediatric listing

	2015	2016
Prevalent patients with severe adult Crohn disease	3,733	4,168
Number of patients switching from the adult to paediatric listing	98	350
Proportion of patients switching listings	2.6%	8.4%

Source: DHS prescriptions database. Accessed on 13 April 2017.

Analysis of expenditure

Commonwealth expenditure on bDMDs to treat Crohn disease is summarised in Table 8 and Figure 8. There was a steady growth in expenditure from 2007 to 2015. A 16% statutory price reduction was applied to infliximab's listings from 1 December 2015. Following this, there was a 10.5% reduction in the annual growth in the total expenditure on bDMDs for Crohn disease between 2015 and 2016 (Table 8).

Table 8: Expenditure on bDMD therapy for Crohn disease by indication and by drug

	Severe Crohn			Fistulising Crohn		Paediatric Crohn		Total Crohn disease
	Inflix ($)	Adal ($)	Vedol ($)	Inflix ($)	Adal ($)	Inflix ($)	Adal ($)	($)
2007	1,205,370					95,608		1,300,978
2008	9,987,591	4,186,920				655,264		14,829,775
2009	13,855,304	19,822,719				1,278,383		34,956,406
2010	18,093,409	27,272,281		1,225,010		2,277,511		48,868,211
2011	22,461,247	34,234,197		5,624,015	1,920,108	2,521,470		66,761,037
2012	26,792,579	40,998,386		7,664,945	6,392,210	3,080,502		84,928,622
2013	32,433,898	47,790,939		10,490,349	8,894,332	4,230,808		103,840,326
2014	40,127,415	56,897,993		13,335,954	11,649,770	5,632,438		127,643,570
2015 [a]	46,793,551	64,406,773	1,316,790	16,214,828	14,915,673	6,697,742	481,860	150,827,216
2016 [a]	41,416,092	68,238,747	9,311,278	14,872,966	16,107,761	6,003,773	2,555,346	158,505,963

Note: The expenditure figures are based on the published price. Special pricing arrangements and risk sharing arrangements may apply.
Inflix, infliximab; Adal, adalimumab; Vedol, vedolizumab.
The expenditure figures from 2007 to 2013 were sourced from the 2015 DUSC review of Crohn disease.
[a] Infliximab was subject to a 16% statutory price reduction from 1 December 2015.

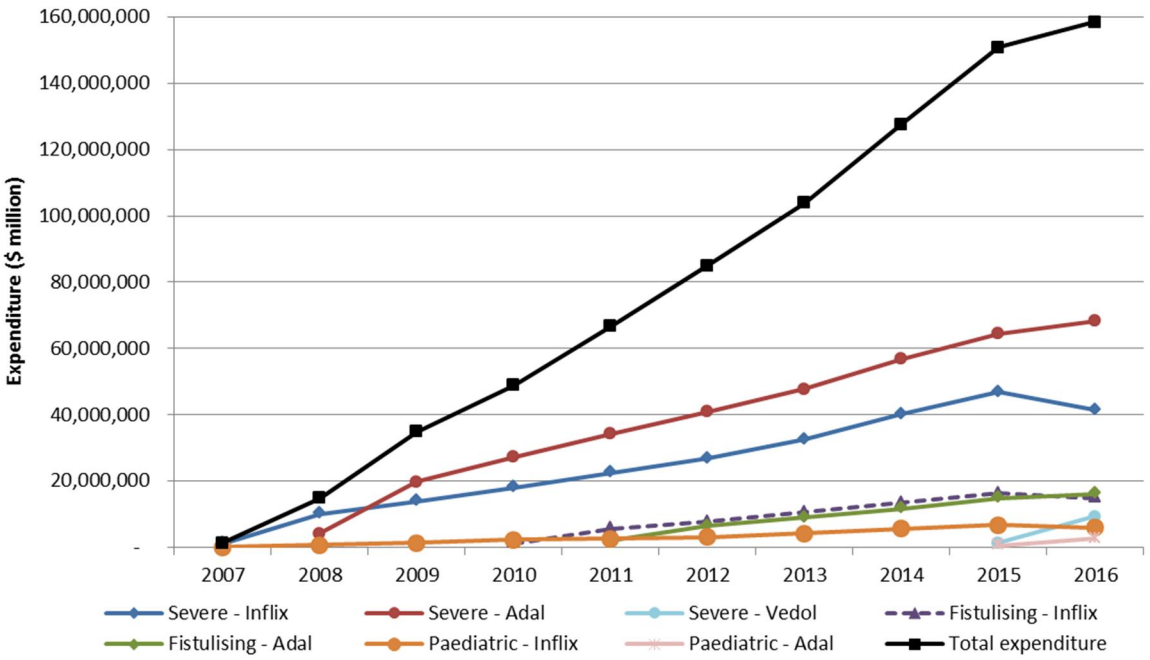

Figure 9: R/PBS expenditure on bDMDs for Crohn disease
Note: Inflix, infliximab; Adal, adalimumab; Vedol, vedolizumab.
The expenditure figures are based on the published price. Special pricing arrangements and risk sharing arrangements may apply.

Discussion

From 2007 to 2016, the number of prevalent patients accessing bDMDs for all of the R/PBS listed indications for Crohn disease increased (Figures 1 to 3 and Tables 2 to 4). There was no indication of a slowing in the growth of bDMD use for any of the Crohn indications. In particular, there was a steady increase in the number of Authority approvals for paediatric Crohn disease following the change in the dosing of corticosteroids for infliximab's listing for this indication and the listing of adalimumab for this indication from August 2015 (Figure 3).

There is limited epidemiological data on Crohn disease in Australia. Available evidence suggests that there are increasing diagnoses in Australia (Day et al., 2014). There was a trend towards an increasing number of incident patients for each Crohn indication (Figures 1 to 3 and Tables 2 to 4). An observational study undertaken in Victoria, Australia reported a point prevalence rate of 344.6 per 100,000 population and an incidence rate of 24.2 per 100,000 population (Studd et al., 2016). As these estimates are specific to the Barwon region in Victoria with a relatively small population, the findings may not apply to the broader Australian community.

The 2015 DUSC review on Crohn disease examined the rates of continuation on bDMDs in patients first initiating on therapy in 2011 for severe refractory adult Crohn disease, fistulising Crohn disease and paediatric Crohn disease. This review extended these analyses for up to five years, corresponding to 10 to 11 Authority approvals for typical patients. The continuation rates were based on the Authorities data because infliximab, being a Highly Specialised Drug listing, did not have complete prescriptions data prior to 1 July 2013. For each Crohn indication, around half of patients had continued on their initiating bDMD for up to 11 Authority approvals (Figures 4, 5 and 6). For severe refractory adult Crohn disease and fistulising Crohn disease, the continuation rates were higher for those patients who switched to an alternative bDMD (Figures 4 and 5).

Vedolizumab was first listed in August 2015 for severe refractory adult Crohn disease. Preliminary data showed that continuation on vedolizumab was similar to the alternative intravenously administered bDMD, infliximab, which has the same frequency of administration, for up to three Authority approvals.

Continuation rates were also examined in a later cohort of patients first initiating on a bDMD in 2014 for each R/PBS listed indication for Crohn disease. Compared with the 2011 initiating cohorts, the continuation rates were similar in the 2014 cohorts for the first four Authority approvals across all of the listed Crohn indications (Figure 8).

Table 9 summarises the response rates from the clinical trials considered in the submissions for infliximab, adalimumab and vedolizumab and continuation assumptions used to inform the financial estimates.

****** Committee-in-confidence ******

Table 9: Clinical trial response rates and continuation assumptions used for the financial estimates

	Trial	Trial-based response rate	Continuation assumptions for the financial estimates
Adult severe refractory Crohn disease			
Infliximab			
Adalimumab			
Vedolizumab			
Fistulising Crohn disease			
Infliximab			
Adalimumab			
Paediatric Crohn disease			
Infliximab			
Adalimumab			

Note: Continuation in this table refers to continuation with the same medicine.

[redacted]

****** End committee-in-confidence ******

The continuation rates for PBS bDMD therapy (Figure 8) were considerably higher than the response rates in the key clinical trials for infliximab, adalimumab and vedolizumab. This could partly relate to the trial response rates being based on continuation on the same medicine whereas patients may switch their therapy under the PBS restrictions. As shown in Figures 4 to 6, a higher proportion of patients who switch to an alternative bDMD remain on therapy for longer than those patients who continue on the same bDMD. Further, the use of complementary immunosuppressive therapy can improve the effectiveness and tolerability of anti-TNF therapy (Hanauer et al., 2002). Differences in the concurrent use of bDMDs with corticosteroids or immunosuppressive therapy between PBS clients and trial participants could potentially be a factor in the variation in continuation rates observed in the clinical trials compared with PBS use.

The use of prior therapy against the PBS restrictions for the adult severe refractory Crohn disease and paediatric Crohn disease indications was examined in patients first initiating on a bDMD in 2016. There were only a small number of cases where a bDMD was first initiated without a record of a prior supply of a corticosteroid or immunosuppressive therapy (azathioprine, 6-mercaptopurine or methotrexate) (Tables 5 and 6). This may represent legitimate use in patients who were contraindicated to these prior therapies. Some paediatric patients recorded as having only received a prior course of a corticosteroid only or immunosuppressive drug only may have also received a course of enteral nutrition.

Adalimumab was first listed for the treatment of severe refractory Crohn disease in children and adolescents from 1 August 2015. Before this listing a small number of patients less than 18 years of age were identified as having been supplied adalimumab under the adult listing for severe refractory Crohn disease (23 patients in 2016). The proportion of patients switching from the adult to paediatric listing for severe Crohn disease in 2016 was 8.4% (Table 7). Of these, 16% of patients were less than 18 years of age (Table 7). The remainder could involve an incorrect entry of the PBS item code.

Expenditure on bDMDs for all R/PBS listed indications for Crohn disease had steadily increased from 2007 to 2016 (Table 8, Figure 9). Based on the published prices, in 2016 the total expenditure was $158.5 million. Severe refractory Crohn disease had a larger treated population compared with fistulising Crohn disease and paediatric Crohn disease. As such, the growth in expenditure was largely driven by infliximab and adalimumab for adult severe refractory Crohn disease (Table 8, Figure 9).

DUSC consideration

DUSC noted that of the adult patients with severe refractory Crohn disease initiating on bDMD therapy in 2011, around 60% remained on treatment after five years. DUSC noted this is much higher than the continuation rates in the clinical trials, which may partly be due to some patients switching to a second (or third) bDMD agent. DUSC commented that the continuation rates in fistulising Crohn disease patients seem high and considered patients may not be ceasing treatment after fistula closure. However, DUSC acknowledged that the restrictions do not include rules or advice of when patients should stop or restart treatment and therefore patients may be receiving continuous treatment.

DUSC noted the analysis of paediatric patients showed a low proportion of patients first supplied a bDMD for moderate to severe paediatric Crohn disease in 2016 did not have a prior R/PBS supply of a corticosteroid or immunosuppressive therapy. DUSC commented that paediatric patients treated in teaching hospitals may not be captured in the analyses.

DUSC noted the comments in the response from the Gastroenterological Society of Australia (GESA) regarding the high continuation rate of Crohn disease patients on anti-TNF therapy compared to clinical trial participants. The response noted:

- The patients entering clinical trials do not represent the real life population with Crohn disease. Many of the patients entering studies are doing so because they have longer duration, more complicated or more refractory to standard therapy disease and this is known to result in lower response rates to anti-TNF therapies. Ha and colleagues report that only 34% of patients would qualify to enter a clinical study (Ha, Ullman, Siegel, & Kornbluth, 2012).
- In clinical trials, use of any additional therapy such as the surgical resection of a stricture, a short course of corticosteroids, bile salt sequestering agents to reduce diarrhoea, anti-diarrhoeal drugs for a short colon or an increase in anti-TNF dose sourced from compassionate access are considered a protocol deviation, whereas under the PBS system these effectively maintain remission at the next assessment point.
- Registration studies for TNF inhibitors only included clinical assessments (CDAI) and biomarker inclusion criteria such as CRP, faecal calprotectin and demonstration of active inflammatory disease at endoscopy, all of which are standard in newer Crohn disease trials. It is well known that anti-inflammatory therapies are ineffective against fibrotic complications such as symptomatic intestinal strictures or against functional symptoms such as irritable bowel syndrome or other mechanical and maldigestive issues like bile salt malabsorption or small bowel intestinal bacterial overgrowth. Clinical practice recognises the importance of thorough assessment of active inflammatory disease and so the patients treated in Australia are likely to have a greater response and persistence rates than the population enrolled in the initial studies.
- Only 25% of patients enrolled in the Accent I infliximab study received concomitant immunosuppression with azathioprine (Hanauer, Feagan, Lichtenstein, & Mayer, 2002). This co-therapy is now recognised to reduce the formation of anti-drug

antibodies against anti-TNF agents and therefore prolong clinical response. The requirements of PBS approval include the use of immunosuppressive agents or intolerance and so therefore a higher percentage of Australian patients were on co-therapy with a likely lowering of immunogenicity and subsequent secondary loss of response.

[redacted]

DUSC considered that if patients with earlier or milder disease will be treated more aggressively, receive bDMDs earlier, and are more likely to receive co-medication of bDMDs and immunotherapy then it is likely the market is not saturated and use will continue to grow. [redacted]

[redacted]

DUSC commented that the use of medicines in this clinical area is likely to continue to increase, particularly as clinical practice is tending to treat earlier stages of disease. DUSC considered it is unknown if cost savings from surgical procedures, such as complete colectomies, has eventuated.

DUSC commented it is unknown if the use of these medicines with higher than expected continuation rates is cost effective. DUSC considered that the coadministration with immunotherapies may be contributing to the longer than anticipated continuation rates of bDMDs. DUSC also considered that other practices, such as patients receiving treatment earlier, may be involved in driving the continuation rates.

DUSC actions

DUSC requested that the report, stakeholder responses and DUSC minutes be provided to the PBAC.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines. The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC. The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines. The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsor comments

Takeda Pharmaceuticals Australia Pty Ltd:

Takeda notes the report's findings the bDMDs are being initiated as per their restrictions for prior therapies in the majority of cases, meaning their use is consistent with the PBAC's recommendations for each of the three medicines, including Takeda's vedolizumab.

AbbVie Pty Ltd:

The sponsor had no comment.

Pfizer Australia Pty Ltd:

The sponsor had no comment.

Janssen-Cilag Pty Ltd:

The sponsor had 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: PBS listing details as at April 2017

Severe refractory Crohn disease

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
05754W	Infliximab, Powder for I.V. infusion 100 mg, 1	1	0	$574.85	Remicade®, Janssen-Cilag Pty Ltd, Inflectra®, Pfizer Australia Pty Ltd
09186L	Adalimumab, Injection 40 mg in 0.8 mL pre-filled syringe, 6, 1	1	0	$4298.62	Humira, Abbvie Pty Ltd
09187M	Adalimumab, Injection 40 mg in 0.8 mL pre-filled pen, 6, 1	1	0	$4298.62	Humira, Abbvie Pty Ltd
09188N	Adalimumab, Injection 40 mg in 0.8 mL pre-filled syringe, 2	2	2	$1508.65	Humira, Abbvie Pty Ltd
09189P	Adalimumab, Injection 40 mg in 0.8 mL pre-filled syringe, 2	2	5	$1508.65	Humira, Abbvie Pty Ltd
09190Q	Adalimumab, Injection 40 mg in 0.8 mL pre-filled pen, 2	2	2	$1508.65	Humira, Abbvie Pty Ltd
09191R	Adalimumab, Injection 40 mg in 0.8 mL pre-filled pen, 2	2	5	$1508.65	Humira, Abbvie Pty Ltd
09613Y	Infliximab, Powder for I.V. infusion 100 mg, 1	1	0	$604.86	Remicade®, Janssen-Cilag Pty Ltd, Inflectra®, Pfizer Australia Pty Ltd
10390W	Vedolizumab, Powder for injection 300 mg, 1	1	0	$3105.19	Entyvio, Takeda Pharmaceuticals Australia Pty Ltd
10415E	Vedolizumab, Powder for injection 300 mg, 1	1	0	$3152.21	Entyvio, Takeda Pharmaceuticals Australia Pty Ltd

Source: the PBS website. Special Pricing Arrangements apply for these listings.

Fistulising Crohn disease

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
08961P	Adalimumab, Injection 40 mg in 0.8 mL pre-filled syringe, 6, 1	1	0	$4298.62	Humira, Abbvie Pty Ltd
08962Q	Adalimumab, Injection 40 mg in 0.8 mL pre-filled pen, 6, 1	1	0	$4298.62	Humira, Abbvie Pty Ltd
08963R	Adalimumab, Injection 40 mg in 0.8 mL pre-filled syringe, 2	2	2	$1508.65	Humira, Abbvie Pty Ltd
08964T	Adalimumab, Injection 40 mg in 0.8 mL pre-filled syringe, 2	2	5	$1508.65	Humira, Abbvie Pty Ltd
08965W	Adalimumab, Injection 40 mg in 0.8 mL pre-filled pen, 2	2	2	$1508.65	Humira, Abbvie Pty Ltd
08966X	Adalimumab, Injection 40 mg in 0.8 mL pre-filled pen, 2	2	5	$1508.65	Humira, Abbvie Pty Ltd
09654D	Infliximab, Powder for I.V. infusion 100 mg, 1	1	0	$574.85	Remicade®, Janssen-Cilag Pty Ltd, Inflectra®, Pfizer Australia Pty Ltd
09674E	Infliximab, Powder for I.V. infusion 100 mg, 1	1	0	$604.86	Remicade®, Janssen-Cilag Pty Ltd, Inflectra®, Pfizer Australia Pty Ltd

Source: the PBS website. Special Pricing Arrangements apply for these listings.

Paediatric Crohn disease

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
05755X	Infliximab, Powder for I.V. infusion 100 mg, 1	1	0	$574.85	Remicade®, Janssen-Cilag Pty Ltd, Inflectra®, Pfizer Australia Pty Ltd
09612X	Infliximab, Powder for I.V. infusion 100 mg, 1	1	0	$604.86	Remicade®, Janssen-Cilag Pty Ltd, Inflectra®, Pfizer Australia Pty Ltd
10389T	Adalimumab, Injection 20 mg in 0.4 mL pre-filled syringe, 2	2	3	$1508.65	Humira, Abbvie Pty Ltd
10396E	Adalimumab, Injection 20 mg in 0.4 mL pre-filled syringe, 2	2	5	$1508.65	Humira, Abbvie Pty Ltd
10397F	Adalimumab, Injection 40 mg in 0.8 mL pre-filled pen, 6, 1	1	0	$4298.62	Humira, Abbvie Pty Ltd
10399H	Adalimumab, Injection 40 mg in 0.8 mL pre-filled syringe, 2	2	0	$1508.65	Humira, Abbvie Pty Ltd
10400J	Adalimumab, Injection 40 mg in 0.8 mL pre-filled pen, 2	2	0	$1508.65	Humira, Abbvie Pty Ltd
10404N	Adalimumab, Injection 40 mg in 0.8 mL pre-filled syringe, 6, 1	1	0	$4298.62	Humira, Abbvie Pty Ltd
10412B	Adalimumab, Injection 40 mg in 0.8 mL pre-filled syringe, 2	2	5	$1508.65	Humira, Abbvie Pty Ltd
10413C	Adalimumab, Injection 40 mg in 0.8 mL pre-filled pen, 2	2	2	$1508.65	Humira, Abbvie Pty Ltd
10419J	Adalimumab, Injection 40 mg in 0.8 mL pre-filled syringe, 2	2	2	$1508.65	Humira, Abbvie Pty Ltd
10420K	Adalimumab, Injection 40 mg in 0.8 mL pre-filled pen, 2	2	5	$1508.65	Humira, Abbvie Pty Ltd
10422M	Adalimumab, Injection 20 mg in 0.4 mL pre-filled syringe, 2	2	0	$1508.65	Humira, Abbvie Pty Ltd

Source: the PBS website. Special Pricing Arrangements apply for these listings.