

# Analysis of medicines used to treat ulcerative colitis

## Drug utilisation sub-committee (DUSC)

June 2017

### **Abstract**

#### **Purpose**

Analysis of medicines for the treatment of ulcerative colitis, including predicted versus actual use of biologics for acute severe and moderate to severe disease.

#### **Listing on the Pharmaceutical Benefits Scheme (PBS)**

Medicines available on the PBS for the treatment of ulcerative colitis include:

- Corticosteroids (prednisolone, hydrocortisone and budesonide in various oral and rectal formulations)
- 5-aminosalicylates (sulfasalazine, mesalazine, balsalazide and olsalazine in a range of oral formulations and rectal formulations)
- Immunomodulators: azathioprine, mercaptopurine, cyclosporin, methotrexate
- Tumour necrosis factor (TNF)-alpha inhibitors (adalimumab, infliximab) and the  $\alpha 4\beta 7$  integrin inhibitor (vedolizumab)

Restrictions apply to some of these medicines. See [pbs.gov.au](http://pbs.gov.au) for details.

#### **Data Source / methodology**

The DHS prescription database was used to identify a cohort of 54,785 patients who were treated for ulcerative colitis between 2012 and 2016.

#### **Key Findings**

- Mesalazine has the highest use of the rectal preparations, the highest use of the oral 5-aminosalicylates, and the highest use overall.
- Budesonide foam enema has not displaced as much of the prednisolone market as expected.
- Use of biologic medicines is low in the context of the entire market of ulcerative colitis, however use is increasing.

## Purpose of analysis

Analysis of medicines for the treatment of ulcerative colitis (UC), including predicted versus actual use of biologics for acute severe and moderate to severe disease.

## Background

### *Clinical situation*

Medicines are used to induce remission in active disease, and then maintain corticosteroid free remission and prevent relapse.<sup>1</sup> The treatment algorithm is determined by the extent and severity of the disease and the location of inflammation within the rectum. Therapy for UC generally involves a step-up approach:

- Mild anti-inflammatory drugs are used at diagnosis;
- After failure on mild anti-inflammatory agents, immunomodulating drugs are used;
- For persistent, active disease antitumour necrosis factor (TNF) and  $\alpha 4\beta 7$  integrin inhibitor drugs are added; and
- If drug therapy fails, surgery is considered.<sup>2</sup>

For the initial therapy of disease flares in UC, 5-aminosalicylic acid (5-ASA) mesalazine preparations are commonly used.<sup>2</sup> 5-ASAs are given rectally or orally. 5-ASA preparations subsidised on the PBS include mesalazine preparations, sulfasalazine, olsalazine and balsalazide. Those available for rectal use include mesalazine enemas (liquid or foam) and suppositories. The PBS restrictions require that patients must first use sulfasalazine before accessing mesalazine unless they are intolerant to sulfasalazine. Side effects to sulfasalazine are mainly from the sulpha moiety which is not present in 5-ASA agents.<sup>2</sup> Sulfasalazine can also cause infertility in males.

Oral steroid therapy, such as prednisolone, is used to treat acute disease flares and in patients unable to take 5-ASA drugs.<sup>2</sup> Oral steroids are not taken recurrently due to their side effects and causing more susceptibility to infection. Corticosteroids can also be administered rectally as enemas, foams and suppositories, and intravenously.

Immunosuppressant drugs are mainly used as maintenance therapy rather than for the induction of remission as they have a slow onset of action.<sup>2</sup> These include thiopurines (azathioprine and 6-mercaptopurine) and methotrexate. The use of immunosuppressants can help to reduce the use of corticosteroids.

Calcineurin inhibitors, including cyclosporin and tacrolimus, are mainly used as rescue therapy for severe episodes of disease which do not responding to high dose intravenous steroids.

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<sup>1</sup> Therapeutic guidelines Published March 2016, eTG March 2017 edition

<sup>2</sup> Australian Guidelines for General Practitioners and Physicians: Inflammatory Bowel Disease. Gastroenterological Society of Australia. Third Edition.

For acute severe UC, patients may access PBS subsidised biological therapy after failing to respond to intravenous corticosteroids. For moderate to severe UC, patients must have failed or be intolerant to a prior course of azathioprine, mercaptopurine or oral corticosteroids.

The TNF-alpha antagonists (adalimumab, infliximab) and the  $\alpha 4\beta 7$  integrin inhibitor vedolizumab may be used for inducing and maintaining remission in patients with moderate to severe active disease who have responded inadequately to standard treatment.

The Therapeutic Guidelines provide guidance on treatment as outlined below.<sup>1</sup>

<b>Active proctitis or distal colitis</b>	
Initial therapy for active proctitis or distal colitis	Mesalazine rectal administration plus 5-ASA orally administered
	If 5-ASA is ineffective, add rectal corticosteroid
Unresponsive active proctitis or distal colitis	Add oral corticosteroid
<b>Extensive ulcerative colitis</b>	
Mild to moderate extensive ulcerative colitis	Oral 5-ASA
	If no response add oral corticosteroid
Moderate to severe chronically active or frequently relapsing ulcerative colitis	If no respond to oral 5-ASA plus corticosteroid or repeated or prolonged courses of corticosteroids are required, consider adding an immunomodulatory medicine such as azathioprine or mercaptopurine
	If azathioprine or mercaptopurine cannot be tolerated consider adding methotrexate
	If no response to a 5-ASA and a corticosteroid after three months (with or without an immunomodulatory medicine), use infliximab or vedolizumab. Combination therapy with infliximab and another immunomodulatory drug (azathioprine, mercaptopurine or methotrexate) may be required. Surgery (proctocolectomy with either ileal pouch–anal anastomosis or end-ileostomy) may be considered for chronic refractory disease.
<b>Acute severe ulcerative colitis</b>	
Acute severe ulcerative colitis is a medical emergency treated in hospital.	
Initial therapy	Fluid, electrolyte or blood replacement when required, together with an intravenous corticosteroid such as hydrocortisone or methylprednisolone sodium succinate.
Salvage therapy	Prompt medical salvage therapy (intravenous cyclosporin or infliximab) or colectomy should be considered for patients with acute severe ulcerative colitis who fail to respond or continue to deteriorate despite 3 to 5 days of intravenous corticosteroid treatment.
<b>Maintenance therapy for ulcerative colitis</b>	
Maintenance	5-ASA orally administered
Maintenance for patients who responded to rectal mesalazine	Mesalazine rectally administered at a reduced frequency
Maintenance for patients with severe initial disease or frequent relapses despite maintenance therapy with 5-ASA	Prolonged remission may be achieved with the addition of an immunomodulatory drug such as azathioprine, mercaptopurine or methotrexate
Chronically active disease that is refractory to the above therapy	Infliximab or vedolizumab if there was a response to induction therapy with these drugs

Source: Therapeutic guidelines, Published March 2016, eTG March 2017 edition

### ***Dosage and administration***

Dosage and administration depends on the medicine, route of administration, formulation, severity and whether treatment is for acute UC or maintenance. Details are provided in Appendix A.

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

### ***PBS listing details (as at April 2017)***

PBS listing details can be found in Appendix B.

### ***Restrictions (abridged)***

The listings for 5-ASA preparations, corticosteroid therapy, immunosuppressant drugs and calcineurin inhibitors are summarised in Table 1.

**Table 1: Listings for 5-ASA preparations, corticosteroid therapy and immunosuppressant medicines**

ORAL 5-ASA	
MESALAZINE	Listings are Authority Required (STREAMLINED)
SULFASALAZINE	Unrestricted listings
BALSALAZIDE	Authority Required (STREAMLINED) listing for ulcerative colitis Patient must have had a documented hypersensitivity reaction to a sulphonamide or patient must be intolerant to sulfasalazine.
OLSALAZINE	Authority Required (STREAMLINED) listing for ulcerative colitis Patient must have had a documented hypersensitivity reaction to a sulphonamide or patient must be intolerant to sulfasalazine.
RECTAL 5-ASA	
MESALAZINE	Suppositories are listed as Restricted Benefit for acute episode of mild to moderate ulcerative proctitis, enemas are listed for acute episode of mild to moderate ulcerative colitis as Authority Required (STREAMLINED)
RECTAL CORTICOSTEROID	
HYDROCORTISONE ACETATE	Restricted Benefit for proctitis and ulcerative colitis
BUDESONIDE	Unrestricted listing
PREDNISOLONE SODIUM PHOSPHATE	Enema is unrestricted listing Suppository is a restricted Benefit for proctitis and ulcerative colitis
ORAL CORTICOSTEROID	
HYDROCORTISONE	Unrestricted listing
PREDNISOLONE	Unrestricted listing
PREDNISOLONE SODIUM PHOSPHATE	Unrestricted listing (oral liquid)
PREDNISON	Unrestricted listing
INJECTABLE CORTICOSTEROID	
HYDROCORTISONE SODIUM SUCCINATE	Unrestricted listing
IMMUNOMODULATORY MEDICINE	
AZATHIOPRINE	Unrestricted listing
MERCAPTOPYRINE	Unrestricted listing
METHOTREXATE	Unrestricted listing
INFLIXIMAB	Acute severe: Authority Required (STREAMLINED) for patients who have failed to achieve an adequate response to at least 72 hours treatment with intravenous corticosteroids
INFLIXIMAB, VEDOLIZUMAB, ADALIMUMAB	Moderate to severe: Authority Required listing for patients who have failed treatment with a 5-aminosalicylate oral preparation, and failed to achieve an adequate response to either azathioprine, mercaptopurine or a tapered course of oral steroids.

The biologics 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.

### Acute severe ulcerative colitis

Patients must be 6 years or older who meet the following criteria:

- Must have a diagnosis of acute severe UC diagnosed by a gastroenterologist or a consultant physician (either internal or general medicine specialising in gastroenterology); and
- must have failed to achieve an adequate response to at least 72 hours treatment with intravenous corticosteroids prior to initiation of biologic treatment in hospital; and
- adults aged 18 years or older must demonstrate a failure to achieve an adequate response to intravenous corticosteroid treatment is defined by the Oxford criteria; or
- for children aged 6 to 17 years, failure to achieve an adequate response to intravenous corticosteroids defined as a PUCAI score greater than 45 at 72 hours.

Prescribers should request the appropriate number of vials, based on the weight of the patient, to provide sufficient for a single infusion at a dose of 5 mg per kg.

### Moderate to severe ulcerative colitis

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

- Must have a diagnosis of moderate to severe UC diagnosed by a gastroenterologist or a consultant physician (either internal or general medicine specialising in gastroenterology); and
- Must have either failed a prior course or be intolerant to azathioprine or 6-mercaptopurine; or
- Must have failed a prior course or be intolerant to oral corticosteroids; and
- a Mayo clinic score greater than or equal to 6 if an adult patient; or
- a patient must have a Paediatric Ulcerative Colitis Activity Index (PUCAI) Score greater than or equal to 30 if aged 6 to 17 years;
- a partial Mayo clinic score greater than or equal to 6, provided the rectal bleeding and stool frequency subscores are both greater than or equal to 2.

For infliximab, 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, or to be administered at 8-weekly intervals for patients who have received prior treatment for an acute severe episode, will be authorised.

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

For adult patients, to receive continuing treatment a patient must have demonstrated or sustained an adequate response to treatment by having a partial Mayo clinic score less than or equal to 2, with no subscore greater than 1. Paediatric patients aged 6 to 17 years must have demonstrated or sustained an adequate response to treatment by having a Paediatric Ulcerative Colitis Activity Index (PUCAI) score of less than 10.

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.

For full details of the current PBS listings refer to the PBS website\_

### **Date of listing on PBS and changes to listing**

Some medicines used to treat UC (hydrocortisone, mercaptopurine, methotrexate, prednisone, prednisolone and sulfasalazine) have been PBS listed since before the beginning of the item history table on 1 May 1964.

**Table 2: PBS listing dates**

<b>Date</b>	<b>Medicine name</b>	<b>Change</b>
1 November 1966	Prednisolone	Suppositories listed
1 December 1968	Azathioprine	First listed for hospital use only
1 August 1984	Hydrocortisone	Rectal foam listed for proctitis and ulcerative colitis
1 August 1988	Olsalazine	First listed as a capsule for inflammatory bowel disease involving the colon in patients with proven hypersensitivity to sulfonamides
1 December 1989	Mesalazine	First listed as a tablet for inflammatory bowel disease involving the colon in patients with proven hypersensitivity to sulfonamides or sustained intolerance to sulfasalazine exists
1 November 1996	Olsalazine	Tablet listed for colitis where hypersensitivity to sulfonamides or intolerance to sulfasalazine exists
1 August 2002	Mesalazine	Sachet containing granules listed for acute mild to moderate ulcerative colitis where hypersensitivity to sulfonamides or intolerance to sulfasalazine exists
1 November 2002	Mesalazine	Enema listed for acute episodes of mild to moderate ulcerative colitis
1 August 2004	Mesalazine	Suppositories listed for acute episode of mild to moderate ulcerative proctitis (not for the treatment of Crohn's disease)
1 December 2004	Mesalazine	Rectal foam listed for acute episode of mild to moderate ulcerative proctitis (not for the treatment of Crohn's disease)
1 August 2005	Balsalazide	Listed for mild to moderate ulcerative colitis where hypersensitivity to sulfonamides exists
1 October 2007	Infliximab	Listed for Crohn disease
1 April 2008	Methotrexate	Restriction for patients requiring doses greater than 20 mg per week
1 August 2008	Adalimumab	Listed for Crohn disease
1 February 2014	Budesonide	Rectal foam listed as an unrestricted listing
1 April 2014	Infliximab	Listed for acute severe ulcerative colitis
1 December 2014	Infliximab	Listed for moderate to severe ulcerative colitis
1 May 2015	Cyclosporin	Restriction was changed from Authority Required to unrestricted listing, prior to this it was not listed for Crohn disease or ulcerative colitis
1 August 2015	Vedolizumab	Listed for severe Crohn disease
1 August 2015	Vedolizumab	Listed for moderate to severe ulcerative colitis
1 December 2016	Adalimumab	Listed for moderate to severe ulcerative colitis

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

### ***Budesonide July 2013***

The PBAC recommended listing of budesonide foam enema as an Unrestricted benefit for treatment of UC on a cost-minimisation basis with prednisolone enema. The accepted equi-effective doses are budesonide 2 mg and prednisolone 20 mg.

The PBAC considered that the submission's estimates of usage were quite low as budesonide was assumed to displace 100% of prednisolone market, and only 10% of the current 5-aminosalicylic acid and hydrocortisone market. The PBAC considered that this was a possible underestimation as it is likely that a higher displacement rate will occur with hydrocortisone because of budesonide's better safety profile.

For further details refer to the Public Summary Document from the July 2013 PBAC meeting.

### ***Infliximab November 2013***

The PBAC recommended extending the listing of infliximab on the PBS under the Section 100 Highly Specialised Drugs Program to include treatment of acute severe ulcerative colitis not responding to IV corticosteroids in a patient aged 6 years or greater, on a cost-minimisation basis compared with cyclosporin. The equi-effective doses estimated are infliximab: 3 infusions at days 0, 14 and 42 of 5 mg/kg and cyclosporin: 7 days intravenously 2 mg/kg followed by 90 days of oral 4 mg/kg.

For further details refer to the Public Summary Document from the November 2013 PBAC meeting.

### ***Infliximab March 2014***

The PBAC recommended the listing of infliximab available as a Section 100 (Highly Specialised Drugs Program) Authority required benefit for the treatment of moderate to severe ulcerative colitis in adults and children.

Infliximab was proposed to be used in patients aged 6 or above with moderate to severe ulcerative colitis, who have failed to achieve an adequate response or have intolerance necessitating permanent treatment withdrawal to conventional therapy such as 5 aminosalicylate and azathioprine/6-mercaptopurine ± corticosteroids.

The submission described infliximab 5 mg/kg as superior in terms of comparative effectiveness and equivalent in terms of comparative safety and tolerability over BSC in the treatment of patients with moderate to severe ulcerative colitis.

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

### ***Vedolizumab March 2015***

The PBAC recommended listing of vedolizumab on a cost-minimisation basis with infliximab for the treatment of moderate to severe ulcerative colitis in adult patients, on the basis that it should be available only as Authority required under the Section 100 Highly Specialised Drugs Program.

The PBAC noted the proposed clinical place for vedolizumab in the re-submission was after failure of the conventional agents (5-ASAs, corticosteroids, and immunomodulators), as for infliximab. The PBAC agreed that switching rules (swapping criteria) within a single treatment cycle must be put in place for infliximab and vedolizumab. The Committee agreed that the restriction should allow a total of 3 trials, where a patient cannot trial and fail or, cease to respond to, the same PBS-subsidised biologics (TNF- $\alpha$  antagonist or  $\alpha$ 4-integrin inhibitor) more than twice.

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

### ***Mesalazine November 2015***

A minor submission to increase the current maximum quantity from 1 pack of 60 tablets to 2 packs of 60 tablets for mesalazine 1.2g modified released tablets for the treatment of ulcerative colitis.

The PBAC accepted the submission's request for the same price per mg (ex-man) noting that this methodology has been accepted for other items in this class. However PBAC considered that there may be grounds to confirm the cost effectiveness of use at higher doses, and asked that Department consider this in any future Post Market Reviews of colitis treatments.

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

### ***Adalimumab March 2016***

The PBAC recommended the listing of adalimumab on the General Schedule for the treatment of moderate to severe ulcerative colitis on the basis of a clinical need for subcutaneous therapy for this condition. In making this recommendation, the PBAC considered that while adalimumab is inferior to infliximab for this indication, listing will allow clinicians to choose from a range of biologics with different modes of administration for the treatment of individual patients. The PBAC considered that the inferiority should be reflected in the pricing of adalimumab.

The PBAC also recommended a flow on change to the current Note for treatment of adult patients with moderate to severe ulcerative to reflect the addition of adalimumab to the PBS-subsidised therapies for this condition. Currently, within the same treatment cycle a patient cannot trial and fail, or cease to respond to, the same PBS-subsidised infliximab or vedolizumab more than twice. As a consequence of the listing of adalimumab, it should be

read as within the same treatment cycle, a patient cannot trial and fail, or cease to respond to, the same PBS-subsidised drug (infliximab, vedolizumab or adalimumab) more than once.

For further details refer to the Public Summary Document from the March 2016 PBAC meeting.

### ***Mesalazine March 2017***

The PBAC recommended the General Schedule Authority Required (STREAMLINED) listing of Asacol (800 mg mesalazine enteric coated tablet) for the treatment of ulcerative colitis on a cost-minimisation basis against the oral formulation of mesalazine on the PBS with the lowest per mg price.

For further details refer to the PBAC outcomes from the March 2017 PBAC meeting.

## **Methods**

The analyses use data from the Department of Human Services (DHS) Authority approvals database and the DHS Medicare Supplied prescriptions database. Authorities data were extracted from January 2012 to March 2017. Prescription data were extracted from January 2012 to December 2016.

The item codes were determined from the Item History file using ATCs. Respiratory ATCs were excluded. Item codes with form and strength descriptions containing the words "Ointment", "Cream", "Fatty ointment" and "Lotion" were excluded.

The remaining item codes were used to determine the related restriction numbers. The item codes were divided into a group with related restriction numbers, and a group which were only unrestricted items.

Restriction numbers containing the words 'arthritis', 'transplant', 'psoriasis', 'dermatitis', 'proctitis', 'ankylosing', 'nephrotic', 'proctosigmoiditis', and 'infiltration' were excluded. The remaining restriction numbers were determined to relate to listings for Crohn disease, UC, or either. The remaining restriction numbers were then used to determine the required item codes, and the item codes with only unrestricted items were also included. Item codes were identified as rectal items if the form and strength field included the words 'enema', 'rectal', 'suppositories', or 'suppository'.

Using this list of item codes, prescription data were extracted from January 2012 to December 2016. This extraction included many patients who had received systemic steroid treatment for an undetermined condition. Using the lists of relevant restriction numbers, a patient analysis was undertaken to identify patients who had received an authority approval for Crohn disease or UC. Patients were also included in the dataset if they had received a rectal steroid using the item list described above or received balsalazide, mesalazine, or olsalazine.

This data set was then analysed to determine if patients were being treated for UC or Crohn disease. Patients with 100% of authority codes or streamlined codes for UC were

used for patient level analyses. This method may underestimate the number of patients with UC, but ensures analysis of prior therapy is not affected by patients with Crohn disease. This method may also make it appear that the number of initiators is decreasing over time, as patients who initiated in later years are less likely to have received an authority code which relates to UC.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available Department of Human Services (DHS) Medicare date of processing data.<sup>3</sup> The publicly available DHS Medicare data only includes subsidised R/PBS prescriptions with prescriptions under the patient co-payment not included. The DHS Medicare data used in this report includes under co-payment prescriptions from 1 April 2012.

The DUSC database combines data on PBS prescriptions submitted to the Department of Human Services (DHS) for payment of a PBS/RPBS subsidy by the Government with an estimate of under patient co-payment prescriptions based on dispensing data from a sample of pharmacies to the end of August 2012. This was replaced by actual under patient co-payment prescription data from 1 April 2012. The DUSC database includes an estimate of private prescriptions based on dispensing data from a sample of pharmacies to the end of August 2012. An estimate of private prescriptions is not included from 1 September 2012.

From 1 July 2013 there was complete prescription data capture for HSD prescriptions dispensed by public and private hospital pharmacies. The s100 medicines listed for UC, infliximab and vedolizumab, were listed for this indication on 1 April 2014 and 1 August 2015 respectively.

Analyses were undertaken in SAS.

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<sup>3</sup> 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 cohort*

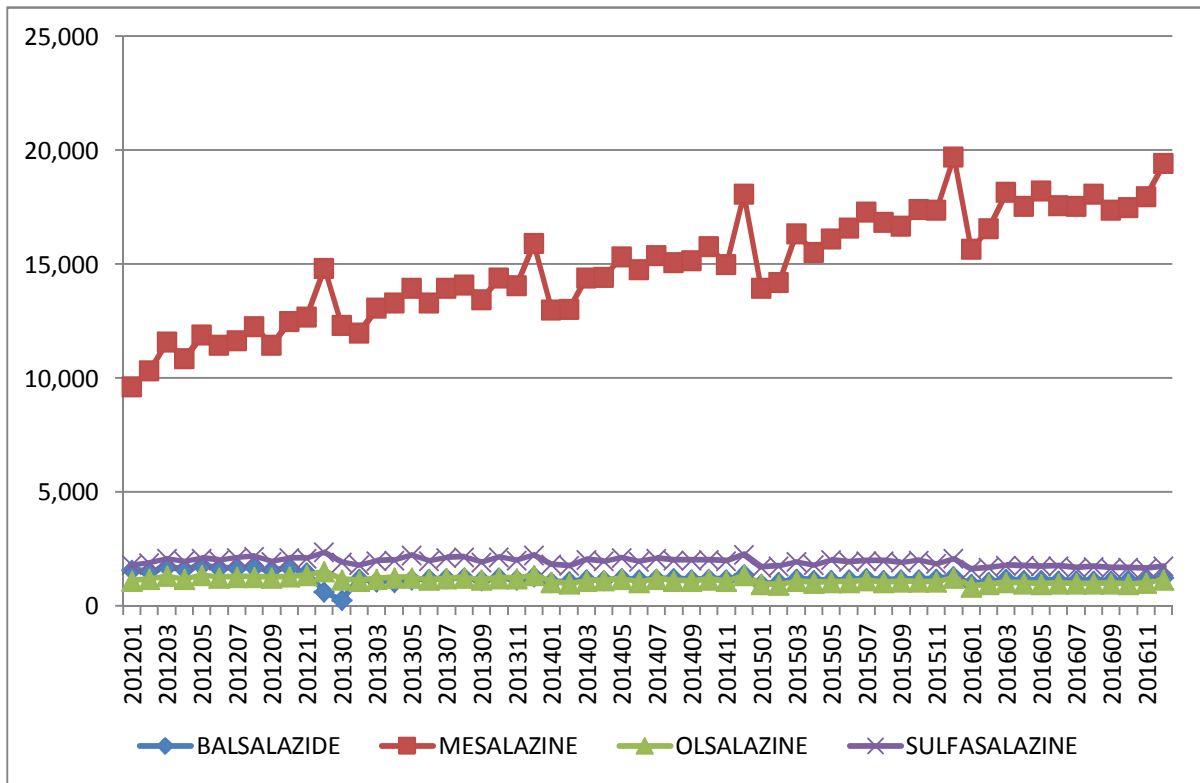
All patients who had a prescription for UC or Crohn disease between 2012 and 2016 were identified. Within this group of patients it was identified some patients had prescriptions with Authority codes for rheumatoid arthritis or psoriatic arthritis. These prescriptions were excluded from the dataset. Then, all Authority codes or streamlined restriction codes for either UC or Crohn disease were identified. This report analyses the medicine use of the cohort of 54,785 patients with 100% of restriction codes indicating use is for UC.

**Table 3: Determination of UC cohort**

<b>Patient group</b>	<b>Number</b>
Patients without an identifying authority or restriction code	22,719
All codes were for UC	54,785
All codes were for Crohn disease	15,394
Codes were a mixture of UC and Crohn disease	13,879
Total patients	106,777

#### *Overall utilisation*

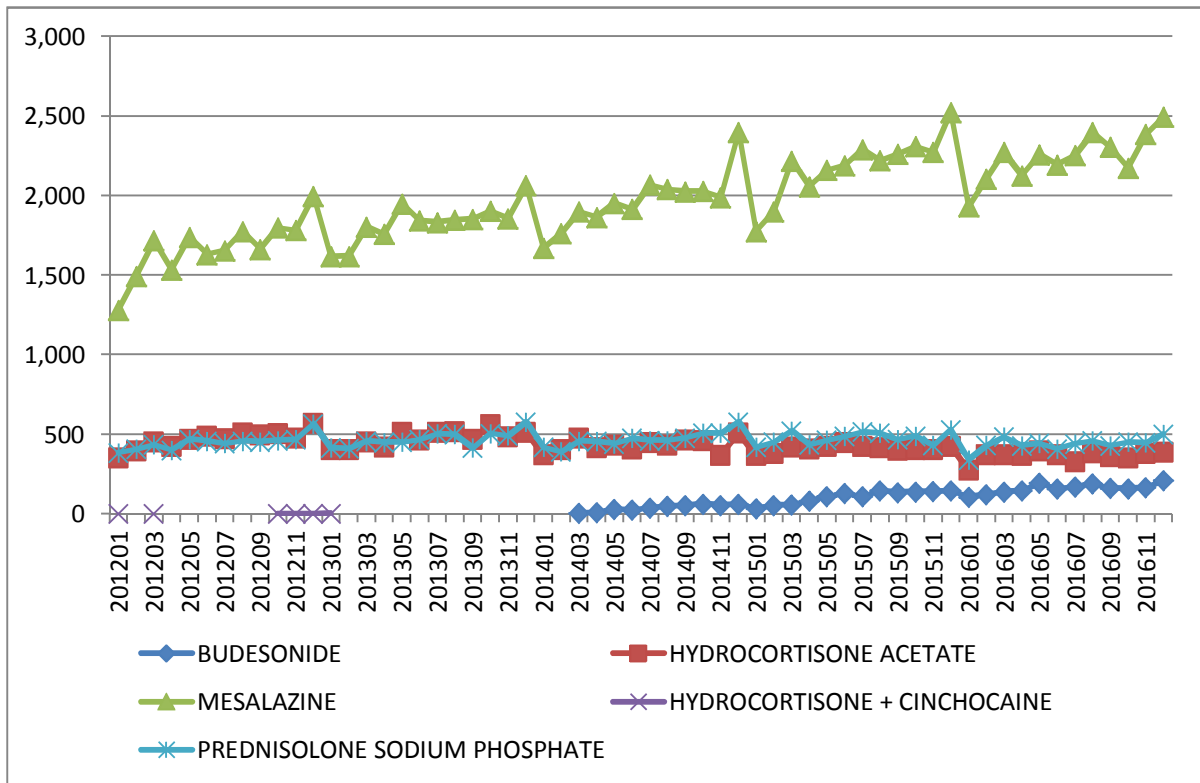
Medicine use for the cohort of 54,785 patients with 100% of restriction codes for UC is shown in Figures 1 to 5. As there are many medicines which can be administered by different methods to treat UC, the medicines have been grouped and presented according to their place in therapy.



**Figure 1: Prescriptions for UC patients of 5-ASAs administered orally**

Use of mesalazine dominates the oral 5-ASA market in the treatment of UC. The PBS restrictions state oral mesalazine, balsalazide and olsalazine should be tried after failure of sulfasalazine.

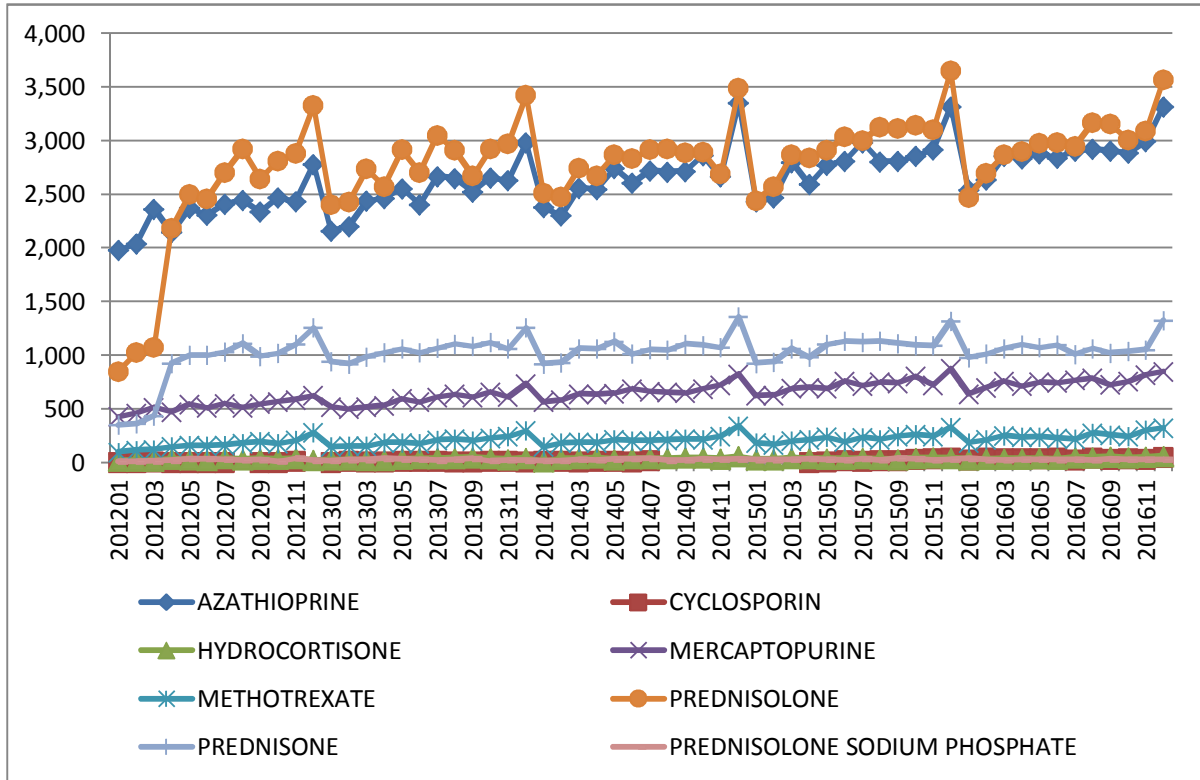
Across all forms, mesalazine is the highest use medicine by at least a factor of 5.



**Figure 2: Prescriptions for medicines for UC administered rectally, by month**

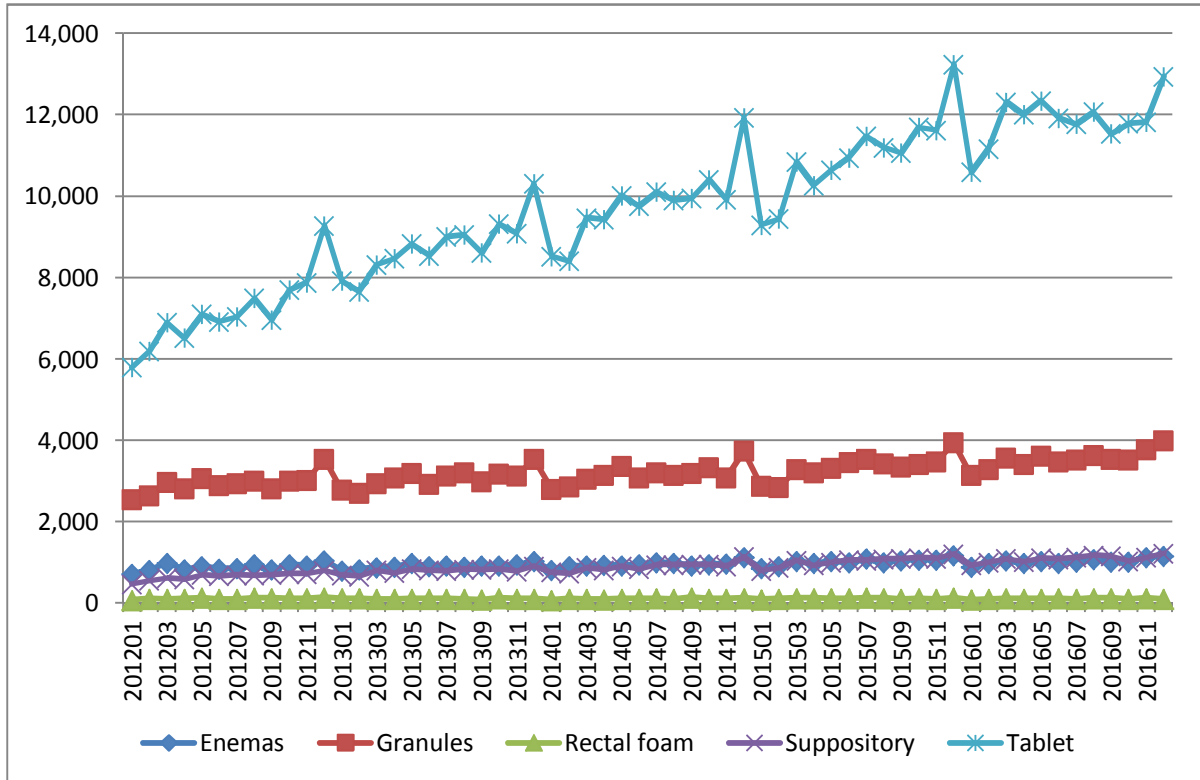
The 5-ASA mesalazine has the highest use of the rectal preparations.

The introduction of the budesonide foam enema does not appear to have affected the overall market. It was predicted that the listing of the budesonide foam enema would displace 100% of the prednisolone market, and 10% of the current 5-ASA and hydrocortisone market. It appears that the use of the prednisolone and hydrocortisone rectal items has decreased, slightly, with hydrocortisone decreasing more than prednisolone. The prednisolone and hydrocortisone rectal items continue to be supplied more than the budesonide foam enema.



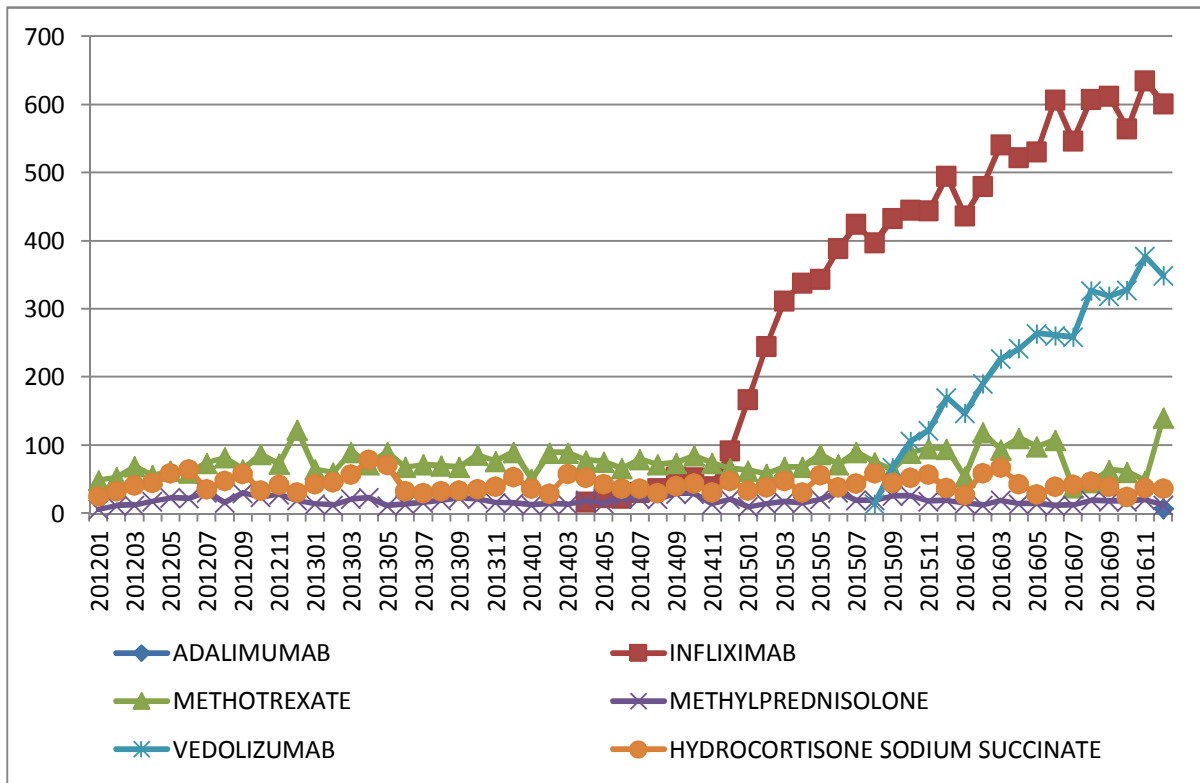
**Figure 3: Prescriptions for UC patients of oral corticosteroids and immunomodulatory medicines**

Figure 3 shows prescriptions of oral corticosteroids and immunomodulatory medicines. Azathioprine is the most commonly used oral immunomodulatory medicines, and prednisolone is the most commonly used oral corticosteroids within the market of UC patients.



**Figure 4: Use of mesalazine by form with the UC cohort of patients**

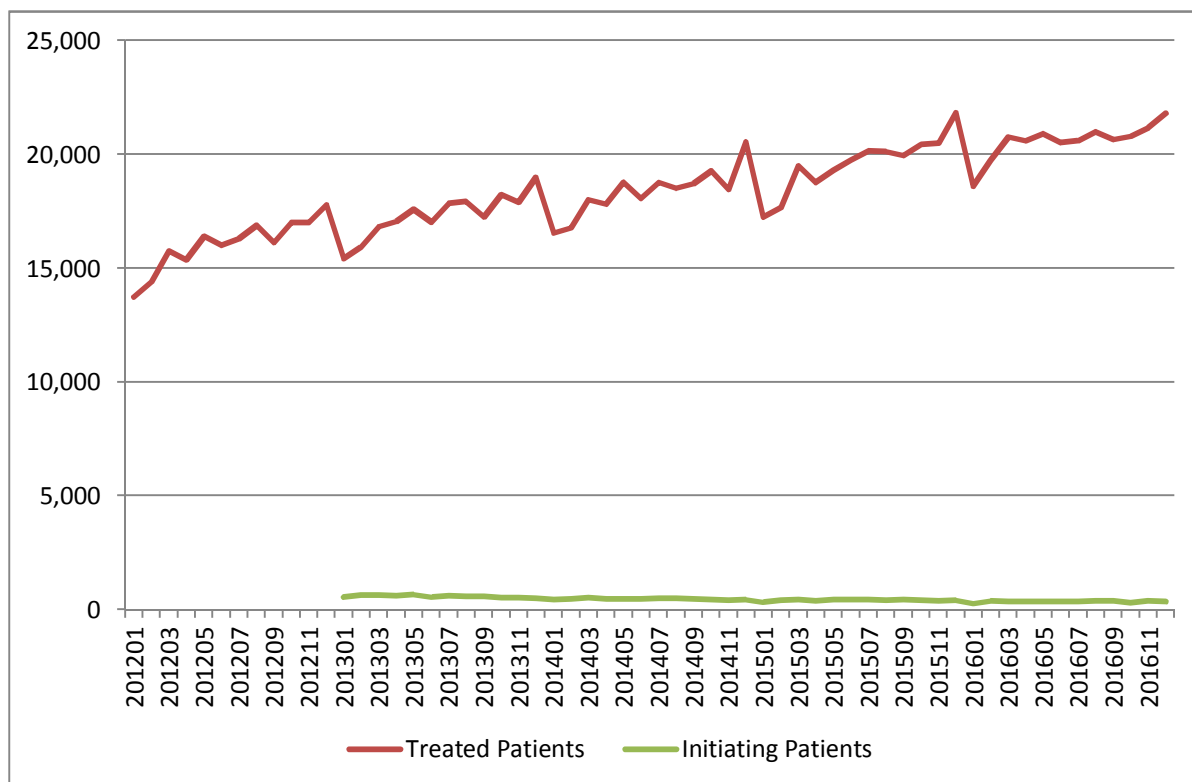
The high use of oral mesalazine (tablets and granules) reflects the use of mesalazine for maintenance treatment. The patient or clinician choice of the form of rectal mesalazine to prescribe will most likely depend on the location of the inflammation.



**Figure 5: Prescriptions for medicines for UC administered as IV infusions or injections, by month**

Use of the parenteral corticosteroids appears to be low and stable, but much of the use of these medicines would be for hospital inpatients, so this is likely to only represent a subset of overall use.

The uptake of infliximab and vedolizumab for acute severe and moderate to severe UC, which is discussed further in the analysis of predicted versus actual utilisation. Only one month of adalimumab utilisation was captured in the data as it was PBS listed on 1 December 2016.



**Figure 6: Initiating and treated patients over time**

The number of initiating patients from the beginning of 2013, with a one year look back, appears stable. This likely reflects the chronic nature of the disease. The slight downward trend of initiating patients is likely due to the selected cohort biasing towards more recently initiated patients not being included in the cohort as they have not received an authority (either for an Authority Required or Streamlined Authority prescription) for UC.

**Prescriber type**

The 10 most common prescriber types for the first prescription of patients who initiated in 2016 is shown in Table 4.

**Table 4: 10 most common prescriber types for initiators in 2016**

Prescriber type	Number of Patients
Gastroenterology and Hepatology	2169
VRGP	817
NONVRGP	342
Internal Medicine	216
Surgery	206
GP Unclassified	131
GP Trainee	46
Paediatric Medicine	39
Not reported	25
Rheumatology	12

### **Treatment sequence**

The 10 most common drug sequences for the cohort who initiated therapy in 2015 is shown in Table 5, using a 12 month follow up. This analysis excludes switching or coadministration as a sequence and only lists each medicine once in each sequence. Use of non-systemic steroids have not been included in the analysis.

**Table 5: The 10 most common treatment sequences for initiators in 2015**

<b>Drug sequence</b>	<b>Number of Patients</b>
MESALAZINE	1,638
PREDNISONE/PREDNISOLONE -> MESALAZINE	627
MESALAZINE -> PREDNISONE/PREDNISOLONE	315
SULFASALAZINE -> MESALAZINE	290
PREDNISONE/PREDNISOLONE	178
PREDNISONE/PREDNISOLONE -> SULFASALAZINE -> MESALAZINE	176
PREDNISONE/PREDNISOLONE -> MESALAZINE -> AZATHIOPRINE	72
HYDROCORTISONE -> MESALAZINE	71
SULFASALAZINE -> MESALAZINE -> PREDNISONE/PREDNISOLONE	70
MESALAZINE -> PREDNISONE/PREDNISOLONE -> AZATHIOPRINE	64

The majority of patients in this cohort who use a 5-ASA in their first 12 months of treatment use mesalazine. A smaller proportion of patients initiate on sulfasalazine and subsequently use mesalazine. Patients only using sulfasalazine are not presented because sulfasalazine is unrestricted and these patients would be identified as “Patients without an identifying authority or restriction code.”

## Analysis of expenditure

Table 6 shows expenditure for medicines for UC using the cohort of 54,785 UC patients.

**Table 6: Expenditure of medicines for UC using UC cohort**

	2012	2013	2014	2015	2016
ADALIMUMAB					\$39,073 <sup>a</sup>
AZATHIOPRINE	\$700,555	\$599,335	\$557,639	\$450,017	\$377,631
BALSALAZIDE	\$2,186,599	\$1,548,258	\$1,617,045	\$1,528,082	\$1,386,081
BUDESONIDE			\$73,996	\$227,914	\$315,304
CYCLOSPORIN	\$10,393	\$31,712	\$19,819	\$53,229	\$114,082
HYDROCORTISONE	\$8,212	\$9,758	\$12,351	\$12,079	\$14,149
HYDROCORTISONE + CINCHOCAINE	\$157	\$46			
HYDROCORTISONE ACETATE	\$83,736	\$113,881	\$91,685	\$83,985	\$67,863
HYDROCORTISONE SODIUM SUCCINATE	\$6,964	\$6,169	\$4,826	\$5,511	\$4,624
INFLIXIMAB			\$1,120,177	\$14,012,592	\$16,729,389
MERCAPTOPYRINE	\$1,401,134	\$1,565,405	\$1,803,757	\$1,966,778	\$1,911,431
MESALAZINE	\$34,186,713	\$40,125,113	\$44,413,259	\$48,204,995	\$51,203,949
METHOTREXATE	\$60,821	\$76,651	\$90,097	\$110,514	\$131,755
METHYLPREDNISOLONE	\$4,413	\$3,793	\$3,563	\$3,194	\$2,985
OLSALAZINE	\$1,553,530	\$1,462,589	\$1,361,139	\$1,250,513	\$1,093,325
PREDNISOLONE	\$65,296	\$69,245	\$68,084	\$102,177	\$116,533
PREDNISOLONE SODIUM PHOSPHATE	\$548,458	\$560,047	\$520,144	\$476,082	\$417,183
PREDNISON	\$30,284	\$29,077	\$30,553	\$41,340	\$46,943
SULFASALAZINE	\$738,380	\$727,272	\$709,033	\$663,526	\$575,420
VEDOLIZUMAB				\$1,483,942	\$10,196,022
<b>Grand Total</b>	<b>\$41,613,574</b>	<b>\$46,966,522</b>	<b>\$52,521,588</b>	<b>\$70,706,105</b>	<b>\$84,756,179</b>

Note: based on published prices

a: Adalimumab expenditure in 2016 is calculated from the full dataset rather than the cohort.

Table 6 shows expenditure for the cohort as treatment for UC includes medicines that are Restricted Benefit and Unrestricted listings. In the complete dataset it would not be possible to determine the reason for prescribing the unrestricted medicines.

Based on the published prices (which are higher than the effective prices paid for drugs subject to special pricing arrangements), the cost of medicines with Authority Required restrictions, calculated from the entire dataset, is approximately 5% to 10% higher than the cost shown in Table 6. The cost of mesalazine in 2016 was \$59 million. This represents a difference of 15%.

## **Analysis of actual versus predicted utilisation**

### ***Approach taken to estimate utilisation***

#### ***Infliximab***

Infliximab was listed for acute severe UC in April 2014, and for moderate to severe UC in December 2014. The November 2013 submission for acute severe UC presented a cost minimisation analysis. This submission used an epidemiological approach to estimate the number of hospitalised UC episodes where patients will fail to respond to IV corticosteroids.

The March 2014 submission for moderate to severe UC submission presented a cost utility analysis. It used an epidemiological approach to estimate the number of patients with moderate to severe disease.

#### ***Vedolizumab***

The March 2015 submission for vedolizumab requested listing on a cost-minimisation basis with infliximab for the treatment of moderate to severe UC in adult patients. It used an epidemiological approach to estimate the number of patients with moderate to severe disease, and calculated cost offsets due to reduced use of infliximab. It applied a prevalent pool of patients in 2014 which it estimated was ████████ of the Australian population. It estimated the rate of incidence for UC was ████████ in 2015 and 2016, and ████████ thereafter.

### ***Analysis of actual versus predicted utilisation***

Analysis of actual versus predicted utilisation was completed using the complete dataset, using PBS item codes to identify prescriptions for UC.

#### ***Infliximab – acute severe ulcerative colitis***

The submission for infliximab for acute severe UC used an epidemiological approach. It applied a prevalence rate of UC of 0.17% to the Australian population aged 6 and over. DUSC had considered the previous submission and recommended using an annualised proportion of patients hospitalised among the prevalent pool. The submission applied an annualised rate for episodes of acute severe UC of ████████ to the prevalent population and assumed ████████ vials of infliximab would be required for each infusion.

The table below counts the number of treated patients and the number of initiating patients. The difference between these counts may suggest the number of patients being treated for subsequent episodes in later years, but will also count patients who suffer a single episode (multiple prescriptions) over the end of one year and beginning of another.

The number of prescriptions was lower than expected in early years, and higher than predicted in 2016.

The submission estimated [REDACTED] of use of infliximab for acute severe disease would occur in public hospitals, and [REDACTED] in private hospitals. The actual use has been between 60% and 70% for public, and 30% to 40% for private hospitals.

**Table 7: Infliximab acute severe disease predicted versus actual**

		2014	2015	2016	2017	2018
Episodes	Predicted	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Patients	Initiating	250	297	423		
	Treated	250	333	473		
	Difference	[REDACTED]	[REDACTED]	[REDACTED]		
Prescriptions	Predicted	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Actual	440	621	905		
	Difference	[REDACTED]	[REDACTED]	[REDACTED]		
Average number of vials per infusion	Predicted	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Actual	4.107	4.137	4.219		
	Difference	[REDACTED]	[REDACTED]	[REDACTED]		
Public/private split (prescriptions)	Public	297 (67.5%)	432 (69.57%)	567 (62.65%)		
	Private	143 (32.5%)	189 (30.43%)	338 (37.35%)		

***Infliximab and vedolizumab for moderate to severe ulcerative colitis***

Infliximab was listed for moderate to severe UC on 1 December 2014. Vedolizumab was listed 1 August 2015. Adalimumab was listed 1 December 2016 and is not included in this analysis.

The three drugs have identical restrictions and patients are allowed to change medicines or re-commence of treatment after a break in therapy. Patients may be prescribed any of these drugs if that patient has previously been issued with an authority prescription for adalimumab, infliximab or vedolizumab for UC in their current treatment cycle.

**Table 8: Predicted versus actual use of infliximab and vedolizumab for moderate to severe ulcerative colitis**

		2014	2015	2016	2017	2018
<b>Actual</b>						
Infliximab	Patients	41	1,009	1,385		
	Prescriptions	54	4,434	6,525		
Vedolizumab	Patients		218	812		
	Prescriptions		600	3,738		
Total	Patients	41	1,147	2,038		
	Prescriptions	54	5,034	10,263		
<b>Predicted</b>						
<b>Infliximab</b>						
Predicted	Patients					
Difference						
Predicted	Prescriptions					
Difference						
<b>Vedolizumab</b>						
Predicted	Patients					
Difference						
Predicted	Prescriptions					
Difference						

Note: Expenditure calculations are using published price.

The differences between counted patients overall and for infliximab and vedolizumab suggest 80 patients in 2015 and 159 patients in 2016 received both drugs.

**Infliximab**

Overall the use of infliximab has been lower than the size of the total market predicted in its original submission.

**Vedolizumab**

The use of vedolizumab was approximately a third of predicted in 2015, as it was listed in August 2015. The estimate of uptake of the number of prescriptions and the cost to Government in 2016 appear accurate.

**Summary**

Overall the use of biologics for the moderate to severe indication has been lower than expected, noting the rate of increase in Figure 5, use may reach predicted levels in the near future.

## Discussion

Inflammatory bowel disease includes UC and Crohn disease, the primary distinguishing feature of these diseases is the location of the inflammation. Patients' disease may worsen over time or the location of the inflammation may change or spread, which may change the diagnosis. This makes it difficult to determine use for each condition within the PBS data as it is necessary to differentiate between the use for these conditions.

The selected cohort does contain some bias, as patients who initiated earlier are more likely to be identified as being Crohn or UC patients, and are more likely to have legitimately been treated for both conditions. Patients initiating later are less likely to have been prescribed an Authority Required or Streamlined Authority medicine, and therefore will not have been identified as a Crohn or UC patient. It is also biased towards not including patients who have only received unrestricted medicines.

The analysis of initiating and treated patients showed the number of treated patients per month is much higher than the number of initiating patients. This is reflective of the nature of UC as a chronic disease, and the likeliness of patients with the disease to be treated.

The main initiating cohort was selected from 2015, to allow 12 months of follow up. Within the cohort of UC patients, 4,080 patients initiated therapy for UC in 2016. Using the 2016 Australian population of 24,128,876 people, this equates to an incidence rate of 0.0169%.

Use of mesalazine is approximately five times higher than other medicines for UC. At least half of the patients who initiated treatment for UC in 2015 initiated on mesalazine. It has the highest use of the medicines administered orally, and the highest use of the medicines administered rectally.

Use of biologics for UC is low but growing.

## DUSC consideration

DUSC noted the use of all forms of mesalazine are increasing, particularly the tablets. DUSC noted the number of prescriptions and cost to Government of mesalazine is much higher than biologics.

DUSC noted the analysis of prior use showed there was a high proportion of patients who did not trial sulfasalazine prior to being supplied mesalazine. DUSC questioned whether this pattern of use indicates a need to reconsider the cost-effectiveness of mesalazine in this population.

DUSC noted the comments in the response from the Gastroenterological Society of Australia (GESA) regarding the comparatively small number of patients who have a prior course of sulfasalazine before commencing therapy with mesalazine. The response noted:

- The European Crohn's and Colitis third evidence based consensus on the management of ulcerative colitis and the Cochrane Library review of oral 5-

aminosalicylic acid state that mesalazine is no more effective than sulfasalazine (RR for failure to achieve remission 0.90, 95% CI 0.77–1.04) but is better tolerated [RR for an adverse event 0.48, 95% CI 0.36–0.63]. 29% of sulfasalazine patients experienced an adverse event compared to 15% of mesalazine patients (RR 0.48, 95% CI 0.37 to 0.63) (Wang, Parker, Bhanji, Feagan, & Macdonald, 2016). It is the tolerance and safety issues for sulfasalazine that are likely driving the greater use of mesalazine.

- Prior sulphur drug reactions are a contraindication to the use of sulfasalazine and many patients are unaware of their prior exposure to sulphur containing agents, but have a recollection of prior adverse reactions to antibiotics as a child.
- The requirement for more intense monitoring of potential adverse events to sulfasalazine also needs to be taken into consideration when assessing the total cost to the Australian community of these agents. The cost of consultation to facilitate this testing also needs to be taken into account.
- The common large reduction in sperm count and reversible azospermia is also a significant consideration in the prescription of sulfasalazine. The peak age of onset for inflammatory bowel diseases is between the ages of 15 and 40 years of age, the peak reproductive years. Many males wish to avoid the potential effect of sulfasalazine to decrease their fertility.
- While equivalent efficacy in the clinical trial environment has been demonstrated, the large pill burden associated with sulfasalazine is an issue for many patients.
- The increased cost to the PBS is clearly apparent from this low rate of sulfasalazine prescription but the adverse events, risk of serious life threatening toxicity, decreased fertility, cost of monitoring; and a high pill burden (with likely lower adherence from treatment with sulfasalazine) should also be taken into account.

DUSC noted the increasing use of mesalazine and questioned whether this increase is due to higher patient numbers or patients using higher doses of mesalazine. DUSC considered it may be necessary to analyse the dosing of mesalazine, whether dosing has changed over time, and investigate the cost-effectiveness of mesalazine. DUSC considered whether an analysis of prescribed doses from MedicinesInsight data may be useful. However DUSC noted that gastroenterologists are the most common prescribers for ulcerative colitis patients, and these specialist prescribers are not captured in the MedicinesInsight data.

DUSC noted the use of methotrexate was higher than might be expected, and commented immunotherapies may be co-prescribed with biologics to improve response and/or reduce antidrug antibodies, but noted that no data has been provided to the PBAC to support this use.

DUSC noted the use of biologics presented in the report and noted it is unclear if use will continue to increase or stabilise. DUSC commented that a few more years of data would be needed to understand the trend of use of these medicines.

DUSC noted that the response from the sponsor of the originator brand of infliximab (Janssen) suggested the market is saturated. The response stated an analysis of the MBS and PBS linked dataset conducted by Prospection suggested that since the introduction of

infliximab on the PBS for ulcerative colitis in 2014, there has been a downward trend in the number of patients having a complete colectomy. The response did not provide data to allow the committee to verify this trend.

DUSC noted the comments in the PSCR from Aspen (Orphan) which sponsors several medicines for the treatment of ulcerative colitis. The sponsor commented there appears to be a trend developing toward prescribing higher doses of mesalazine. The sponsor noted the recommended dose, based on clinical evidence, is 2-3 g per day, but it has been observed that some patients who do not respond to the recommended dose have responded to higher doses of mesalazine. The sponsor considered this should apply to a small proportion of ulcerative colitis patients, but stated it has been reported more than half of ulcerative colitis patients are currently using 4 g or more per day. The sponsor expressed support for the PBAC confirming the cost-effectiveness of the use of higher doses of mesalazine for mild to moderate ulcerative colitis.

## **DUSC actions**

- DUSC considered that an analysis of the dosing trends for mesalazine would be informative.
- DUSC requested that the report be provided to the PBAC.

## **Context for analysis**

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

## **Sponsors' comments**

Takeda Pharmaceuticals Australia Pty Ltd: Takeda notes that its estimation of the number of prescriptions for vedolizumab and its cost to Government in 2016 appeared accurate. Takeda also notes that in terms of expenditure on UC medicines, mesalazine represents at

least 60% of the overall expenditure when the published prices of the biological agents are used. In comparison, the use and cost of the biologic medicines is low.

AbbVie Pty Ptd, Alphapharm, Alphapharm Pty Ltd, Amneal Pharmaceuticals Pty Ltd, Apotex Pty Ltd, Arrow Pharma Pty Ltd, Aspen Pharmaceuticals Australia Pty Ltd, Baxter Healthcare Pty Ltd, Clinect Pty Ltd, Eris Pharmaceuticals Australia Pty Ltd, Ferring Pharmaceuticals Pty Ltd, Fresenius Kabi Australia Pty Ltd, Generic Health Pty Ltd, iNova Pharmaceuticals Australia Pty Ltd, Janssen-Cilag Pty Ltd, Link Medical Products Pty Ltd, Meda Pharmaceuticals Pty Ltd, Merck Sharp & Dohme, Novartis Pharmaceuticals, Orphan Australia Pty Ltd, Pfizer Australia Pty Ltd, Sandoz Pty Ltd, Shire 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

Details are from the relevant Product Information, or the Australian Medicines Handbook where indicated.

**Table 9: Dosage and administration of medicines for ulcerative colitis**

Brand name and sponsor	Product	Dose and frequency of administration
Salazopyrin® Pfizer Australia Pty Ltd Pyralin Ena® Pfizer Australia Pty Ltd Salazopyrin-EN® Pfizer Australia Pty Ltd	Sulfasalazine	Initial Dosage Adults: 1 to 2 g four times daily. Children: 40 to 60 mg/kg bodyweight daily in three to six divided doses. Maintenance Dosage Adults: 2 g daily in four divided doses. Children: 40 mg/kg bodyweight daily in four divided doses. The daily maintenance dose should be continued unless contraindicated by side effects. should be given preferably after meals in evenly divided doses over a 24 hour period with no more than 8 hours between overnight doses. The enteric coated tablets should not be crushed or broken.
Dipentum® Clinect Pty Ltd	Olsalazine	Olsalazine should be taken at regular intervals during the day, after meals. Adults: Long Term Maintenance of Remission Adults including the elderly: 1g/day (2 capsules or 1 tablet, twice daily), to be continued indefinitely. Adults: Acute Ulcerative Colitis Adults including the elderly: Normal dose 2 g/day, in divided doses.
Colazide® Fresenius Kabi Australia Pty Limited	Balsalazide	Capsules should be swallowed whole with food. Adults Treatment of active disease: 3 capsules three times daily until remission or for 12 weeks maximum. Maintenance treatment: 2 capsules twice daily. The dose can be adjusted based on each patient's response. An additional benefit has been shown with a dose of 8 capsules daily. Rectal or oral steroids can be given concomitantly if necessary.
Pentasa® Ferring Pharmaceuticals Pty Limited Mesasal® Aspen Pharmacare Australia Pty Limited Salofalk® Orphan Australia Pty Ltd Mezavant® Shire Australia Pty Limited	Mesalazine	Orally: Tablets: Acute disease: <u>1.5 g to 4.8 g</u> g per day taken once daily or in divided doses. The dosage can be adjusted in accordance with the response to treatment. Maintenance therapy: 1.5 g to 2.4 g per day taken once daily or in divided doses.  Granules: For adults and the elderly: Unless otherwise prescribed, the recommended dose for acute ulcerative colitis is 1.5 g to 4 g per day. For maintenance of remission for ulcerative colitis, the

Brand name and sponsor	Product	Dose and frequency of administration
		<p>recommended dose is 1.5 g to 2 g per day.            For children older than 6 years of age:            The recommended dose for acute ulcerative colitis, depending on disease severity, is 30-50 mg mesalazine/kg/day. For maintenance of remission and/or long term treatment of ulcerative colitis, the recommended dose is 15-30 mg mesalazine/kg/day.</p>
<p>Salofalk® Orphan Australia Pty Ltd            Pentasa® Ferring Pharmaceuticals Pty Limited</p>	<p>Mesalazine</p>	<p>Rectally:            Enema and foam enema: Unless otherwise advised a dose of 1 g, 2 g or 4 g mesalazine enema once a day is used for the treatment of acute ulcerative colitis or maintenance of remission.            The content of one enema bottle (1 g/100mL, 2 g/30 mL, 2 g/60 mL, or 4 g/60 mL) is instilled in the rectum once every evening prior to going to bed.             Suppository: One 1 g suppository should be inserted into the rectum once daily at bedtime. The best results are achieved if the bowels are evacuated prior to insertion of suppository.</p>
<p>Predsol® Aspen Pharma Pty Ltd</p>	<p>Prednisolone suppositories</p>	<p>Contain prednisolone 5 mg. Administer twice daily, one at bedtime and the other after morning defecation.</p>
<p>Predsol® Aspen Pharma Pty Ltd</p>	<p>Prednisolone retention enema</p>	<p>One enema contains prednisolone 20 mg/100 mL, use one enema nightly on retiring, for two to four weeks.</p>
<p>Sone® iNova Pharmaceuticals (Australia) Pty Limited</p>	<p>Prednisone</p>	<p>Adults: 10 to 100 mg daily in divided doses.            Children: 1 to 5 years. 2.5 to 10 mg twice daily. 6 to 12 years: 5 to 20 mg twice daily.</p>
<p>Panafcort® Predsone® Aspen Pharmacare Australia Pty Limited</p>	<p>Prednisone</p>	<p>Adults: The initial adult dosage may range from 20 to 40 mg daily, but can be 60 to 80 mg daily if necessary, depending on the disease being treated. Maintenance dosage: Usually 5 to 20 mg daily.            In long term therapy the ideal dosage should not be greater than 40 mg per day so as to minimise side-effects. It is usually administered in 2-4 divided doses or as a single daily dose after breakfast or on alternate days.            Children: Initial dosage: 0.5 mg/kg daily in three or four divided doses after food as in adults. This dosage can be doubled or trebled if necessary. Maintenance dosage: 0.125 to 0.25 mg/kg daily.</p>
<p>Budenofalk® Orphan Australia Pty Ltd</p>	<p>Budesonide</p>	<p>Apply one actuation of 2 mg budesonide daily. Budesonide 2 mg foam enema can be applied in the morning or evening.</p>
<p>Colifoam® Meda Pharmaceuticals Pty Ltd</p>	<p>Hydrocortisone</p>	<p>Rectally            The dosage is one applicator full containing approximately 90 to 100 mg hydrocortisone acetate, as directed by the doctor. The usual dosage rate is one applicator full once or twice daily for two to three weeks, and every second day thereafter, applied as directed above into the rectum.</p>

Brand name and sponsor	Product	Dose and frequency of administration
Hysone 4 <sup>®</sup> Hysone 20 <sup>®</sup> Alphapharm Pty Ltd Solu-Cortef <sup>®</sup> Pfizer Australia Pty Ltd	Hydrocortisone	Systemic: Orally: Dosage requirements are variable and must be individualised on the basis of the disease and the response of the patient. IV injection: Therapy is initiated by administering hydrocortisone powder for injection intravenously over a period of 30 seconds (e.g., 100 mg) to 10 minutes (e.g., 500 mg or more).
Purinethol <sup>®</sup> Aspen Pharmacare Australia Pty Limited Allmercap <sup>®</sup> Link Medical Products Pty Ltd	Mercaptopurine	Adult 1-1.5 mg/kg daily Child > 2 years, 1-1.5 mg/kg once daily. Maximum 50 mg daily initially; may be increased to 75 mg daily. Round doses to nearest half tablet (25 mg) (AMH)
Various brands and manufacturers	Azathioprine	Adult, child, oral 1-3 mg/kg daily in 1 or 2 doses; adjust according to response (AMH)
Sandimmun <sup>®</sup> Neoral <sup>®</sup> Neoral 10 <sup>®</sup> Neoral 25 <sup>®</sup> Neoral 50 <sup>®</sup> Neoral 100 <sup>®</sup> Novartis Pharmaceuticals Australia Pty Limited Cyclosporin Sandoz <sup>®</sup> Sandoz Pty Ltd	Cyclosporin	Adult, IV 2 mg/kg daily as a continuous infusion. Adjust dose according to patient response and whole blood concentration. Change to oral cyclosporin after inducing remission. (AMH)
Humira <sup>®</sup> AbbVie Pty Ltd	Adalimumab	Induction 160 mg Initial Dose (Day 0) as four injections OR as two injections on Day 0 and two injections on Day 1 80 mg Second Dose (Day 14) as two injections Maintenance 40 mg Starting Day 28 & continuing fortnightly
Remicade <sup>®</sup> Janssen- Cilag Pty Ltd Inflectra <sup>®</sup> Pfizer Australia Pty Ltd	Infliximab	Adults and in children and adolescents (6 to 17 years) 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion dose at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.
Entyvio <sup>®</sup> Takeda Pharmaceuticals Australia Pty Ltd	Vedolizumab	Adults (≥18 years) The recommended dose regimen of vedolizumab is 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight 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.

Source: Product Information <https://www.ebs.tga.gov.au/>  
Australian Medicines Handbook, 2016

## Appendix B

### *PBS listing details (as at April 2017)*

**Table 10: PBS listing of April 2017**

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
10961X	Adalimumab, Injection 40 mg in 0.8 mL pre-filled pen, 2	2	5	\$1,401.30	Humira VE
10955N	Adalimumab, Injection 40 mg in 0.8 mL pre-filled pen, 2	2	2	\$1,401.30	Humira VE
10945C	Adalimumab, Injection 40 mg in 0.8 mL pre-filled pen, 6, 1	1	0	\$3,987.46	Humira VE
10960W	Adalimumab, Injection 40 mg in 0.8 mL pre-filled syringe, 2	2	5	\$1,401.30	Humira VE
10944B	Adalimumab, Injection 40 mg in 0.8 mL pre-filled syringe, 2	2	2	\$1,401.30	Humira VE
10972L	Adalimumab, Injection 40 mg in 0.8 mL pre-filled syringe, 6, 1	1	0	\$3,987.46	Humira VE
02688L	Azathioprine, Tablet 25 mg, 100	100	5	\$22.72	Various brands and manufacturers
02687K	Azathioprine, Tablet 50 mg, 100	100	5	\$31.27	Various brands and manufacturers
10034D	Budesonide, Rectal foam 2 mg per application, 14 applications, aerosol 16.8 g, 2, 1	1	3	\$188.11	Budenofalk OA
Various	Cyclosporin, Capsule various strengths	Various	5	\$79.84 to \$546.40	Various brands and manufacturers
06125J	Cyclosporin, Oral liquid 100 mg per mL, 50 mL, 1	4	5	\$1,310.18	Neoral NV
05633L	Cyclosporin, Oral liquid 100 mg per mL, 50 mL, 1	4	5	\$1,263.16	Neoral NV
08661W	Cyclosporin, Oral liquid 100 mg per mL, 50 mL, 1	2	3	\$707.10	Neoral NV
05631J	Cyclosporin, Solution concentrate for I.V. infusion 50 mg in 1 mL, 10	10	0	\$54.10	Sandimmun NV
06109M	Cyclosporin, Solution concentrate for I.V. infusion 50 mg in 1 mL, 10	10	0	\$65.12	Sandimmun NV

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
01510L 05118J	Hydrocortisone, Injection 100 mg (as sodium succinate) with 2 mL solvent, 1	6	0	\$39.96	Solu-Cortef PF
03470P 01501B	Hydrocortisone, Injection 100 mg (as sodium succinate) with 2 mL solvent, 1	2	0	\$20.36	Solu-Cortef PF
03471Q 03096Y	Hydrocortisone, Injection 250 mg (as sodium succinate) with 2 mL solvent, 1	1	0	\$19.32	Solu-Cortef PF
01511M 05119K	Hydrocortisone, Injection 250 mg (as sodium succinate) with 2 mL solvent, 1	6	0	\$63.12	Solu-Cortef PF
01502C	Hydrocortisone, Rectal foam containing hydrocortisone acetate 90 mg per applicatorful, 14 applications, aerosol 21.1 g, 1	2	3	\$40.14	Colifoam HM
01500Y	Hydrocortisone, Tablet 20 mg, 60	60	4	\$31.20	Hysone 20 AF
01499X	Hydrocortisone, Tablet 4 mg, 50	50	4	\$25.02	Hysone 4 AF
10184B	Infliximab, Powder for I.V. infusion 100 mg, 1	1	0	\$604.86	Remicade JC
10057H	Infliximab, Powder for I.V. infusion 100 mg, 1	1	1	\$604.86	Remicade JC
10067W	Infliximab, Powder for I.V. infusion 100 mg, 1	5	1	\$2,874.25	Inflectra PF
10184B	Infliximab, Powder for I.V. infusion 100 mg, 1	1	0	\$604.86	Inflectra PF
10057H	Infliximab, Powder for I.V. infusion 100 mg, 1	1	1	\$604.86	Inflectra PF
10196P	Infliximab, Powder for I.V. infusion 100 mg, 1	1	0	\$574.85	Inflectra PF
10067W	Infliximab, Powder for I.V. infusion 100 mg, 1	5	1	\$2,874.25	Remicade JC
10196P	Infliximab, Powder for I.V. infusion 100 mg, 1	1	0	\$574.85	Remicade JC
10214N	Mercaptopurine, Oral suspension 20 mg per mL, 100 mL, 1	1	2	\$434.54	Allmercap LM
01598D	Mercaptopurine, Tablet 50 mg, 25	100	2	\$242.54	Purinethol AS

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
08753Q	Mesalazine, Enemas 1 g in 100 mL, 7, 1	4	1	\$310.86	Pentasa FP
08616L	Mesalazine, Enemas 2 g in 60 mL, 7, 1	4	1	\$310.86	Salofalk OA
08617M	Mesalazine, Enemas 4 g in 60 mL, 7, 1	4	1	\$418.66	Salofalk OA
08768L	Mesalazine, Rectal foam 1 g per applicatorful, 14 applications, aerosol 80 g, 1	4	1	\$310.86	Salofalk OA
08599N	Mesalazine, Sachet containing granules, 1 g per sachet, 100	100	5	\$255.20	Salofalk OA
09206M	Mesalazine, Sachet containing granules, 1.5 g per sachet, 60	60	5	\$221.07	Salofalk OA
10257W	Mesalazine, Sachet containing granules, 3 g per sachet, 30	30	5	\$221.07	Salofalk OA
08598M	Mesalazine, Sachet containing granules, 500 mg per sachet, 100	200	5	\$272.70	Salofalk OA
02234N	Mesalazine, Sachet containing prolonged release granules, 1 g per sachet, 120	120	5	\$305.38	Pentasa FP
02287J	Mesalazine, Sachet containing prolonged release granules, 2 g per sachet, 60	60	5	\$287.32	Pentasa FP
10254Q	Mesalazine, Sachet containing prolonged release granules, 4 g per sachet, 30	30	5	\$287.32	Pentasa FP
05461K	Mesalazine, Suppository (moulded) 1 g, 30	30	1	\$122.81	Salofalk OA
08752P	Mesalazine, Suppository 1 g, 30	30	1	\$122.81	Pentasa FP
03413P	Mesalazine, Tablet 1 g (prolonged release), 60	120	5	\$305.38	Pentasa FP
09353G	Mesalazine, Tablet 1.2 g (prolonged release), 60	120	5	\$390.82	Mezavant ZI
01611T	Mesalazine, Tablet 250 mg (enteric coated), 100	100	5	\$85.71	Mesasal AS
08731M	Mesalazine, Tablet 500 mg (enteric coated), 100	200	5	\$272.70	Salofalk OA
02214M	Mesalazine, Tablet 500 mg (prolonged release), 100	200	5	\$272.70	Pentasa FP

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
01920C	Prednisolone, Enema, retention, 20 mg (as sodium phosphate) in 100 mL, 7	28	3	\$197.74	Predsol QA
08285C	Prednisolone, Oral solution 5 mg (as sodium phosphate) per mL, 30 mL, 1	1	5	\$17.76	PredMix LN and Redipred AS
02554K	Prednisolone, Suppositories 5 mg (as sodium phosphate), 10, 1	3	3	\$41.34	Predsol QA
Various	Prednisolone and prednisone, various strengths	Various	4	\$13.07 to \$14.90	Various brands and manufacturers
10398G	Vedolizumab, Powder for injection 300 mg, 1	1	0	\$3,152.21	Entyvio TK
10384M	Vedolizumab, Powder for injection 300 mg, 1	1	0	\$3,105.19	Entyvio TK

Source: the PBS website.