

5.03 MESALAZINE, Tablet (enteric coated) 800 mg, Asacol[®], Baxter Australia Pty Ltd.

1 Purpose of Application

- 1.1 The submission requested a General Schedule Authority Required (Streamlined) listing for Asacol (800 mg mesalazine enteric coated tablet) for the treatment of ulcerative colitis.

2 Requested listing

- 2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
MESALAZINE mesalazine 800 mg enteric tablet, 90	2	5	\$390.81	Asacol® Baxter Australia

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Ulcerative colitis
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have had a documented hypersensitivity reaction to a sulphonamide, OR Patient must be intolerant to sulfasalazine.
Administrative Advice	Note <i>Not for the treatment of Crohn disease</i> Note <i>Continuing Therapy Only:</i> <i>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.</i>

- 2.2 The listing was requested on a cost-minimisation basis compared to Mezavant (1.2 g mesalazine prolonged release tablet).

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

- 3.1 **TGA status at time of PBAC consideration:** Asacol (800 mg mesalazine enteric coated tablet) is TGA-approved for the treatment of mild to moderate ulcerative colitis and maintenance of remission in adults. A lower strength of Asacol (400 mg mesalazine enteric coated tablet) is also approved but was not included in the submission for PBS listing.

- 3.2 Asacol has not previously been considered by the PBAC for the treatment of ulcerative colitis.
- 3.3 There are six other oral formulations of mesalazine already listed on the PBS for the treatment of ulcerative colitis marketed under four proprietary names (i.e. Mezavant tablets, Pentasa tablets and granules, Salofalk tablets and granules, and Mesasal tablets) as summarised in Table 1.

Table 1: Summary of PBS-listed oral formulations of mesalazine

Brand (active ingredient)	Formulation	Recommended dose		Frequency of administration
		Induction	Maintenance	
Asacol (mesalazine)	Enteric coated tablets, pH \geq 7.0 release	2.4 g to 4.8 g	1.6 g to 2.4 g	Once daily or in divided doses. Doses >2.4 g per day must be administered in divided doses
Mezavant (mesalazine)	Gastro-resistant prolonged release tablets, pH \geq 7.0 release	2.4 g to 4.8 g	2.4 g	Once daily
Pentasa ^a (mesalazine)	Prolonged release tablets	Up to 4 g	2 g	Once daily or in divided doses
	Prolonged release granules	Up to 4 g	2 g	Once daily or in divided doses
Salofalk ^a (mesalazine)	Gastro-resistant prolonged release tablets, pH \geq 6.0 release	1.5 g to 3 g	1.5 g	Once daily or in divided doses
	Gastro-resistant prolonged release granules, pH \geq 6.0 release	1.5 g to 3 g	1.5 g	Once daily or in divided doses
Mesasal ^a (mesalazine)	Enteric coated tablets, pH \geq 6.4	1.5 g	0.75 g	Divided doses

Source: Table 2, p3 and Figure 2, p8 of the submission, Asacol, Mezavant, Pentasa, Salofalk and Mesasal Product Information

- 3.4 Any further reference to Asacol in this document refers to the 800 mg mesalazine enteric coated tablet formulation. The different oral formulations of mesalazine are also referred to using proprietary names.

4 Clinical place for the proposed therapy

- 4.1 Mesalazine belongs to the 5-aminosalicylic acid (5-ASA) class of drugs used for the treatment of ulcerative colitis, a chronic inflammatory bowel condition characterised by relapsing and remitting episodes limited to the colon. Asacol is an enteric coated tablet, formulated to be gastro-resistant that releases at the terminal ileum and colon (pH 7 and above).
- 4.2 The proposed treatment algorithm was a simplified representation of the treatment options for patients with ulcerative colitis. The algorithm is consistent with the proposed restriction but wider than the approved TGA indication as use of mesalazine is not limited to adults with mild to moderate disease.

- 4.3 The submission positioned Asacol as a treatment alternative to other oral formulations of mesalazine used as first-line treatment in the induction of remission or maintenance therapy for ulcerative colitis. The recommended daily dose of Asacol is 2.4 g to 4.8 g for induction of remission and 1.6 g to 2.4 g for maintenance of remission. There were differences in recommended doses for each oral mesalazine formulation, with published guidelines suggesting a range of 2.0 g to 4.8 g per day for induction of remission and 1.0 g to 3.0 g daily for maintenance therapy.
- 4.4 Published guidelines do not differentiate between oral formulations of mesalazine although the Gastrointestinal Therapeutic Guidelines 2016 suggests that different brands of mesalazine are not interchangeable, especially if the disease is well-controlled.
- 4.5 The ESC advised that the clinical need for the therapy was unclear. The Pre-Sub-Committee Response (PSCR) claimed that clinicians and patients may prefer the flexibility in dose titration provided by Asacol 800 mg tablets, compared with Mezavant 1.2 g tablets. The ESC advised that this claim had not been sufficiently substantiated given that a dose response was not demonstrated. Specifically there may be no treatment effect difference between high and low dose oral mesalazine treatment for induction of remission, and that there are limited data to support the use of a lower dose (i.e. 1.6 g per day) for maintenance of remission (see “Comparative effectiveness”).
- 4.6 The Pre-PBAC Response reiterated, “the availability of an additional oral tablet formulation of mesalazine may provide a valuable treatment option for some patients with UC”. The Pre-PBAC Response stated that all mesalazine oral tablets have different release properties, which may benefit different patients.
- 4.7 In terms of dose titration, the PBAC agreed with the ESC that a dose response was not demonstrated, but noted that the 800 mg tablet did allow different doses to be prescribed consistent with the TGA Product Information.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

5 Comparator

- 5.1 The submission claimed that Mezavant 1.2 g tablet was the appropriate comparator based on highest market share compared with other oral mesalazine formulations using PBS utilisation estimates. The PSCR reiterated that Mezavant is the only oral tablet formulation that is reimbursed for ulcerative colitis alone (other brands are also reimbursed for Crohn’s Disease). The ESC advised that while Mezavant has the highest market share, based on information presented in the submission it accounts for less than half of the market. The ESC advised that other less expensive oral formulations of mesalazine (i.e. Salofalk, Pentasa or Mesasal) may also be relevant comparators where used for ulcerative colitis.
- 5.2 The Pre-PBAC Response noted that all randomised trials comparing Asacol with another form of mesalazine were included in the submission. In addition to the three trials versus Mezavant, there is only one trial of Asacol versus another brand of mesalazine available in Australia (Pentasa) and this was presented in the submission

as a supportive study. The Pre-PBAC Response stated that this study demonstrated the superiority of Asacol 3.6 g per day versus Pentasa 2.25 g, and noninferiority of Asacol 2.4 g versus Pentasa 2.25 g for the induction and maintenance of remission (Ito 2010a¹, Ito 2010b²).

- 5.3 The PBAC recalled that mesalazine granules were recommended for listing on the basis of the same price per milligram (mg) compared to the tablets, and that Mezavant was recommended on a cost minimisation basis with Salofalk and Pentasa brands of mesalazine at the same price per mg of mesalazine. The PBAC noted that it could only recommend listing Asacol at a higher price than an alternative therapy or therapies if it is satisfied that it provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. The PBAC considered all oral formulations of mesalazine to be alternative therapies and, as a significant improvement in efficacy or reduction in toxicity had not been demonstrated over other oral formulations, Salofalk and Pentasa were relevant comparators with a lower price per mg of mesalazine compared with Mezavant (see Table 9 below).

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 The submission was based on the following comparisons:
- Induction of remission: a head-to-head trial comparing Asacol 2.4 g versus Mezavant 2.4 g (Kamm 2007)
 - Maintenance of remission: two head-to-head trials comparing;
 - Asacol 2.4 g versus Mezavant 2.4 g (Prantera 2009); and
 - Asacol 1.6 g versus Mezavant 2.4 g (D'Haens 2012).
- 6.4 No comparative data were presented to support the use of high dose Asacol (3.6 g or 4.8 g) for induction of remission.
- 6.5 The submission provided supportive analyses from two systematic reviews (Wang 2016a and Wang 2016b) of oral 5-ASAs (e.g. mesalazine, sulfasalazine, balsalazide and olsalazine) versus placebo. A comparison of active treatments (i.e. oral 5-ASAs,

¹ Ito, H. *et al* (2010a). Direct comparison of two different mesalamine formulations for the induction of remission in patients with ulcerative colitis: a double-blind, randomized study. *Inflammatory Bowel Diseases* 16(9): 1575-1582.

² Ito, H. *et al* (2010b). Direct comparison of two different mesalamine formulations for the induction of remission in patients with ulcerative colitis: a double-blind, randomized study. *Inflammatory Bowel Diseases* 16(9): 1567-1574.

Asacol or Mezavant) versus placebo was presented for both induction and maintenance of remission. Additional subgroup analyses of dose-ranging studies of Asacol 4.8 g versus Asacol 2.4 g and Mezavant 4.8 g versus Mezavant 2.4 g were provided for induction of remission.

- 6.6 No formal indirect analyses were conducted for comparisons using supportive data.
- 6.7 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Induction of remission		
Kamm 2007	Kamm MA, Colombel J, Kornbluth A, et al. A randomised comparison of once- versus twice-daily MMX® mesalamine for the maintenance of remission in mild-to-moderate ulcerative colitis.	Gastroenterology; 2007; 132(4 Suppl 1):A510
Maintenance of remission		
Prantera 2009	Prantera C, Kohn A, Campieri M, et al. Clinical trial: Ulcerative colitis maintenance treatment with 5-ASA: a 1-year, randomized multicentre study comparing MMX with Asacol.	Alimentary Pharmacology and Therapeutics; 2009; 30(9):908-18
D'Haens 2012	D'Haens G, Sandborn WJ, Barrett K, et al. Once-daily MMX® mesalamine for endoscopic maintenance of remission of ulcerative colitis.	American Journal of Gastroenterology; 2012; 107(7):1064-77

Source: Table 8, pp15-17 of the submission

- 6.8 The key features of the direct randomised trials are summarised in Table 3.

Table 3: Key features of the direct randomised trials

Trial	N	Design	Dosing regimen	Risk of bias	Patient population	Outcomes
Induction of remission						
Kamm 2007 (8 weeks)	341	Double-blind, double-dummy multicentre RCT	Mezavant 2.4 g once daily vs. Mezavant 4.8 g once daily vs. Asacol 2.4 g per day (3 divided doses) vs. placebo	High	- Adult - Newly diagnosed or relapsing - Active, mild to moderate ulcerative colitis	Proportion of patients in clinical and endoscopic remission for Mezavant (2.4 g and 4.8 g) vs. placebo at 8 weeks. Secondary objective of safety and tolerability of Mezavant vs. placebo or Asacol.
Maintenance of remission						
Prantera 2009 (12 months)	331	Double-blind, double-dummy multicentre RCT	Mezavant 2.4 g once daily vs. Asacol 2.4 g per day (2 divided doses)	Low	- Adult - Left-sided ulcerative colitis in remission with ≥ 1 relapse ≤ 12 months prior	Proportion of patients in clinical remission, and proportion of patients in clinical and endoscopic remission at 12 months (co-primary outcomes)
D'Haens 2012 (6 months)	826	Double-blind, multicentre RCT	Mezavant 2.4 g once daily vs. Asacol 1.6 g daily (2 divided doses)	Low	- Adult - Ulcerative colitis in remission for ≥ 30 days on a stable dose of mesalazine (≤ 2.4 g daily) or equivalent dose of sulfasalazine (≤ 6.2 g daily)	Proportion of patients with endoscopic remission at 6 months

Source: Table 9, pp20-21 of the submission

Abbreviations: RCT, randomised controlled trial

- 6.9 Overall, the risk of bias for the trials comparing the interventions for maintenance of remission (Prantera 2009 and D'Haens 2012) was low. However, the risk of bias was high in the Kamm 2007 study for induction of remission. Although a central interactive voice response system was used for the majority of treatment allocations, 35 of the 341 recruited patients had forced allocations to the next treatment in the randomisation (e.g. due to delay in medication arrival at the site). There was potential for the randomisation and concealment to be compromised during the study. In the Kamm 2007 study, there was a potential for survivor bias due to differential discontinuation, with more patients in the placebo arm discontinuing compared with the active treatment arms (39.5% vs. 15-19% respectively). The majority of patients discontinued due to lack of efficacy.
- 6.10 There were issues of applicability to the proposed PBS population for all included trials. Kamm 2007 excluded patients previously receiving 5-ASA doses of more than 2.0 g per day or who had recent treatment with rectal or oral steroids. The trial patient population may be more responsive to 5-ASA treatment at lower doses and may be less representative of patients with more severe disease. Prantera 2009 and D'Haens 2012 both excluded patients with severe ulcerative colitis and those previously receiving other treatments (e.g. rectal mesalazine, corticosteroids or immunosuppressants). The trial populations may not be applicable to the PBS population, which could have severe disease based on the proposed restriction and

patients who could be treated with Asacol in combination therapy (e.g. with rectal mesalazine or corticosteroids).

- 6.11 The ESC noted that there were substantial issues of heterogeneity in the Prantera 2009 trial. Study authors conducted an analysis of overall remission rates by country and noted statistically significantly higher proportions of patients in remission in Poland (77.8%) and Ukraine (96.7%) compared with Italy (54.6%). The authors acknowledged the differences between Italy, Poland and Ukraine in the proportion of patients receiving a 5-ASA dose of more than 1.6 g per day (79.2% vs. 49.0% vs. 36.1% respectively).
- 6.12 It was unclear if the formulations used in the included studies were identical to the proposed Asacol tablet in the submission (Kamm 2007 and D'Haens 2012 administered Asacol 400 mg tablets; Prantera 2009 used Asacol 800 mg tablets). The TGA clinical evaluator noted the lack of comprehensive pharmacokinetic data in patients with ulcerative colitis and the observed variations in plasma measure between the 800 mg and 400 mg formulations.
- 6.13 In all trials, there were differences in dosing frequency and pill burden between active treatments. Although the differences in administration had minimal impact within the trials, it is unclear if the higher pill burden and dosing frequency in those receiving Asacol compared with Mezavant will affect compliance in the eligible PBS population.

Comparative effectiveness

- 6.14 Table 4 summarises the main results and post-hoc analysis comparing Asacol 2.4 g versus Mezavant 2.4 g from Kamm 2007 for induction of remission.

Table 4: Induction of remission at 8 weeks, Kamm 2007 (ITT population)

Clinical and endoscopic remission	Asacol 2.4 g N=86	Mezavant 2.4 g N=84	Mezavant 4.8 g N=85	Placebo N=86
Proportion at 8 weeks, n/N (%), p-value for comparison versus placebo	28/86 (32.6) p=0.124	34/84 (40.5) p=0.010	35/85 (41.2) p=0.007	19/86 (22.1)
Comparison vs Mezavant 2.4 g, RR (95% CI)	0.80 (0.54, 1.20)	-	1.02 (0.71, 1.46)	0.55 (0.34, 0.88)
Comparison vs placebo, RR (95% CI)	1.47 (0.89, 2.43)	1.83 (1.14, 2.94)	1.86 (1.09, 3.19)	-

Source: Table 21, p36 of the submission and Kamm 2007 publication

Abbreviations: CI, confidence interval; ITT, intent-to-treat; RR, relative risk

- 6.15 The outcome of clinical and endoscopic remission was based on a modified Ulcerative Colitis Disease Activity Index (UC-DAI), which is a composite score based on four variables: stool frequency, rectal bleeding, mucosal appearance and physician's rating of disease activity. Clinical and endoscopic remission was defined as a total UC-DAI score of not more than 1 based on the component scores summarised in Table 5.

Table 5: Ulcerative Colitis Disease Activity Index (UC-DAI)

Component	Score			
	0	1	2	3
Stool frequency	Normal	1-2 stools/day >normal	3-4 stools/day >normal	>4 stools/day >normal
Rectal bleeding	None	Streaks of blood	Obvious blood	Mostly blood
Mucosal appearance	Normal	Mild friability	Moderate friability	Exudation, spontaneous bleeding
Physician's rating of disease activity	Normal	Mild	Moderate	Severe

Source: Table 19, p34 of the submission

- 6.16 The PBAC has previously considered the outcomes of clinical remission and clinical response for the treatment of moderate to severe ulcerative colitis (March 2014 infliximab PSD, July 2014 adalimumab PSD and March 2015 vedolizumab PSD). The outcomes were based on the Mayo score (composite outcome based on stool frequency, rectal bleeding, sigmoidoscopy and physician's assessment) which is similar to the UC-DAI score.
- 6.17 A lower proportion of patients treated with Asacol 2.4 g achieved induction of remission compared with Mezavant 2.4 g (32.6% vs 40.5%) but the difference was not statistically significant (RR 0.80, 95% CI 0.54, 1.20). Although the results suggest no treatment effect difference between Asacol 2.4 g and Mezavant 2.4 g, results should be interpreted with caution as the study was not powered for noninferiority or a comparison between active treatments.
- 6.18 A higher proportion of patients receiving Asacol 2.4 g achieved induction of remission compared to placebo (32.6% vs. 22.1% respectively) although the difference was not statistically significant (RR 1.47, 95% CI 0.89, 2.43). Patients receiving treatment with Mezavant 2.4 g and 4.8 g had statistically significantly higher induction of remission rates versus placebo (40.5%, p=0.007 and 41.2%, p=0.01 versus 22.1%).
- 6.19 No comparative data were presented to support the use of high dose Asacol (3.6 g or 4.8 g) versus Mezavant for the induction of remission.
- 6.20 Table 6 summarises the main results (mITT population) and post-hoc analysis (ITT population) comparing Asacol 2.4 g with Mezavant 2.4 g from the Prantera 2009 study for maintenance of remission. The outcome for clinical and endoscopic remission was based on a modified UC-DAI score.

Table 6: Maintenance of remission at 12 months, Prantera 2009 study (ITT and modified ITT populations)

	Post-hoc analysis (ITT ^a)		Primary analysis (mITT)	
	Asacol 2.4 g N=169	Mezavant 2.4 g N=162	Asacol 2.4 g N=167	Mezavant 2.4 g N=156
Clinical and endoscopic remission, n/N (%)	103/169 (60.9)	95/162 (58.6)	103/167 (61.7)	95/156 (60.9)
RD (95% CI)	2.3% (-8.3, 12.9)		0.8% (-9.9, 11.4)	
RR (95% CI)	1.04 (0.87, 1.24)		1.01 (0.85, 1.20)	
Clinical remission, n/N (%)	110/169 (65.1)	106/162 (65.4)	110/167 (65.9)	106/156 (68.0)
RD (95% CI)	-0.3% (-10.6, 9.9)		-2.1% (-12.3, 8.2)	
RR (95% CI)	0.99 (0.85, 1.16)		0.97 (0.83, 1.13)	

Source: Table 22, p38 of the submission and Prantera 2009 publication

Abbreviations: CI, confidence interval; ITT, intent-to-treat; mITT, modified intent-to-treat; RD, risk difference; RR, relative risk

^aPost-hoc analysis using ITT/safety population presented in the submission

Results in italics were calculated during the evaluation using data from the Prantera 2009 publication

- 6.21 The submission claimed noninferiority between Asacol 2.4 g and Mezavant 2.4 g for clinical and endoscopic remission based on the lower bound of the 95% confidence interval of -8.3% that did not exceed -10%. The choice of a 10% noninferiority margin was based on at least half the demonstrated superiority of mesalazine in the Mesalamine Study Group trial (Hanauer 1996). In the trial, the difference in endoscopic remission rates between delayed-release mesalazine 1.6 g per day versus placebo was 21.8% (95% CI: 7.6%, 36.1%). The ESC advised that it was unclear whether the chosen noninferiority margin was representative of a minimal clinically important difference.
- 6.22 The difference in clinical remission rates between Asacol 2.4 g and Mezavant 2.4 g arms was not statistically significant based on the post-hoc analysis results (RD -0.3%, 95% CI -10.6%, 9.9%). The primary analysis reported a lower bound for the 95% confidence interval that exceeded -10% but remained less than -15% (RD 2.1%, 95% CI -12.3%, 8.2%).
- 6.23 The submission claimed noninferiority between Asacol 2.4 g and Mezavant 2.4 g for clinical remission based on the lower bound of the 95% confidence interval (-10.6%) from the post-hoc analysis that was borderline at the -10% margin but less than -15%. A review of clinical efficacy endpoints in ulcerative colitis noted that some jurisdictions have accepted a noninferiority margin of 15% for regulatory approval (D'Haens 2007). Based on the margins used in noninferiority trials identified in a systematic review of 5-ASAs in ulcerative colitis (Wang 2016), a noninferiority margin of 10% may be more appropriate.
- 6.24 Overall, the ESC agreed that the results should be interpreted with caution as the trial was designed as a superiority trial and not powered for a noninferiority comparison between Asacol and Mezavant. In addition, the ESC noted the authors' observation of substantial heterogeneity between the study populations in each country within the trial.
- 6.25 Table 7 summarises the post-hoc analysis comparing Asacol 1.6 g with Mezavant 2.4 g from the D'Haens 2012 study for maintenance of endoscopic remission. The primary analysis was a comparison of Mezavant versus Asacol in the per-protocol population with results for the ITT population presented as a sensitivity analysis. The use of the post-hoc analysis had a minimal impact on efficacy results.

Table 7: Maintenance of remission at 6 months, D’Haens 2012 study (post-hoc analysis, ITT population)

	Asacol 1.6 g N=411	Mezavant 2.4 g N=415
Endoscopic remission, n/N (%)	316/411 (76.9)	323/415 (77.8)
RD (95% CI) ^a	-0.9% (-6.6, 4.8)	
RR (95% CI) ^a	0.99 (0.92, 1.06)	

Source: Table 23, p38 of the submission

Abbreviations: CI, confidence interval; ITT, intent-to-treat; RD, risk difference; RR, relative risk

- 6.26 The difference in the proportion of patients achieving endoscopic remission in those receiving Asacol 1.6 g compared with Mezavant 2.4 g was not statistically significant (RD -0.9%, 95% CI -6.6%, 4.8%).
- 6.27 The submission claimed noninferiority between Asacol 1.6 g and Mezavant 2.4 g based on the lower bound of the 95% confidence interval of -0.9%(-6.6, 4.8) that did not exceed -10%. Although the results support the submission’s claim, the clinical relevance of remission defined by endoscopic results alone was unclear. The PSCR argued that secondary endpoints (maintenance of mucosal healing with no or mild symptoms, time to relapse, modified UC-DAI score, safety and tolerability) in the D’Haens study (D’Haens 2012) support the conclusion that Asacol 1.6 g provides the same health outcomes as Mezavant 2.4 g in the maintenance of remission of ulcerative colitis.
- 6.28 Overall, the clinical evidence comparing the efficacy of Asacol and Mezavant in induction and maintenance of remission was of low quality. No comparative data were presented for the use of high dose Asacol for induction of remission. The supportive data were inconsistent, with a pooled subgroup analysis from a systematic review (Wang 2016a) suggesting that Asacol (1.6-4.8 g) was superior to placebo and the Kamm 2007 trial suggesting Asacol 2.4 g was no different to placebo. The ESC noted that a pooled subgroup analysis of trials (Wang 2016a) further suggests no treatment effect difference between high (4.8 g) and low (2.4 g) dose oral mesalazine treatment for induction of remission (see table below).

Table 8: Pooled subgroup analysis of Asacol 4.8 g versus Asacol 2.4 g from Wang 2016a for induction of remission

	Hanauer 2005		Hanauer 2007		Sandborn 2009	
	Asacol 4.8 g N=191	Asacol 2.4 g N=195	Asacol 4.8 g N=147	Asacol 2.4 g N=154	Asacol 4.8 g N=389	Asacol 2.4 g N=383
Failure to induce global or clinical remission or improvement, n/N (%)	79/191 (41)	93/195 (48)	71/147 (48)	77/154 (50)	116/389 (30)	132/383 (34)
RR (95% CI)	0.87 (0.69, 1.08)		0.97 (0.77, 1.22)		0.87 (0.70, 1.06)	
Asacol 4.8 g vs Asacol 2.4 g, Pooled RR (95% CI)					0.89 (0.78, 1.01)	
Chi-square for heterogeneity: 0.61, df=2, P=0.74						
I ² statistic with 95% uncertainty interval = 0%						

Source: Table 31, p47 of the submission and Analysis 5.2, p130 of Wang 2016 publication

Abbreviations: CI, confidence interval; RR, relative risk

- 6.29 Systematic reviews comparing oral 5-ASAs including mesalazine, sulfasalazine, balsalazide and olsalazine (Wang 2016a, Wang 2016b and Ford 2011) with placebo had consistent results, suggesting that 5-ASAs were superior to placebo for both induction and maintenance of remission. However, the authors acknowledged substantial heterogeneity between trials (e.g. disease severity, trial duration, efficacy endpoints). Many of the studies were early preliminary trials and had a high risk of bias. The TGA clinical evaluator noted that although there was adequate data to support the use of Asacol 2.4 g to 4.8 g per day for induction of remission and 2.4 g per day for maintenance therapy, there were limited data supporting the use of a lower dose (i.e. 1.6 g per day) for maintenance of remission.

Comparative harms

- 6.30 There was limited detail in the safety data reported in the trial publications. The authors noted no differences between the proportions of patients experiencing adverse events between treatment arms within the trials. Overall, the safety profile of Asacol was consistent with the known safety profile of oral mesalazine. The majority of the reported treatment-related adverse events were gastrointestinal disorders (e.g. ulcerative colitis, abdominal pain) or headache and there were no reports of serious treatment-related events in the trials.

Clinical claim

- 6.31 The submission described Asacol as noninferior in terms of efficacy and safety compared with Mezavant. During the evaluation, it was considered that the efficacy claim was not adequately supported because:
- Data presented to support the claim of noninferiority of Asacol 2.4 g and Mezavant 2.4 g for induction of remission may not be reliable (high risk of bias, limited applicability and trial not powered for noninferiority or a comparison between active treatments).
 - No comparative data were presented to support the use of high dose Asacol (3.6 g or 4.8 g per day) for induction of remission. The supportive data in the submission did not show statistically significant differences between mesalazine 4.8 g and 2.4 g for induction of remission.
 - The evidence provided to support the claim of noninferiority of low dose Asacol 1.6 g compared with Mezavant 2.4 g for maintenance of remission may not be reliable given the primary outcome of endoscopic remission. The clinical importance of endoscopic remission and whether there is an association with patient-relevant outcomes is unclear.
 - The relative efficacy of Asacol 2.4 g and Mezavant 2.4 g for maintenance of remission was unclear given the uncertainties and low quality of the clinical evidence (substantial heterogeneity, trial not powered for noninferiority, uncertainty whether the chosen noninferiority margin was representative of a minimum clinically important difference, and limited applicability).
- 6.32 During the evaluation, it was considered that the safety claim may be reasonable despite limited data as the safety profile for mesalazine is well-established.
- 6.33 The PBAC considered that the claim of noninferior comparative effectiveness to Mezavant was uncertain but accepted it based on the totality of the evidence presented.

- 6.34 The PBAC considered that the claim of noninferior comparative safety was reasonable as the safety profile of Asacol was consistent with the known safety profile of oral mesalazine.

Economic analysis

- 6.35 The submission presented a cost-minimisation analysis. The equi-effective doses estimated based on head-to-head trials comparing Asacol and Mezavant are as follows:
- Induction of remission: Asacol 2.4 g = Mezavant 2.4 g
 - Maintenance of remission: Asacol 1.6-2.4 g = Mezavant 2.4 g
- 6.36 The submission also proposed an equi-effective dose based on a claim of no difference in efficacy between high dose and low dose mesalazine:
- Induction of remission: Asacol 4.8 g = Mezavant 4.8 g
- 6.37 The submission proposed an equivalent ex-manufacturer price for Asacol based on Mezavant, using the same price per mg of mesalazine. The approach was similar to the Mezavant listing which was recommended on a cost-minimisation basis with Salofalk and Pentasa at the same price per mg of mesalazine (Mezavant Web Outcome, November 2009). The same price per mg approach was used in the recommendation of mesalazine granules when compared with mesalazine tablets (PBS Therapeutic Relativity Sheets, November 2016).
- 6.38 The ESC did not consider the clinical data to be adequate to support equivalence between Asacol and Mezavant on a milligram to milligram basis.
- 6.39 A comparison of price per mg and price per day (based on minimum and maximum recommended doses) of Asacol and other PBS-listed oral formulations of mesalazine show variation in the price per mg and price per day. This was largely dependent on the recommended dose (e.g. Mesasal maintenance treatment dose of 750 mg costs \$2.10 per day; Mezavant 2.4 g costs \$5.79 per day) as summarised in Table 9.

Table 9: Summary of ex-manufacturer prices of oral formulations of mesalazine

Brand	Strength and formulation	AEMP	Price per mg	Induction		Maintenance	
				Dose	Price per day	Dose	Price per day
Asacol	800 mg tablets	\$173.68	\$0.00241	2.4-4.8 g	\$5.79 to \$11.58	1.6-2.4 g	\$3.86 to \$5.79
Mezavant	1.2 g tablets	\$173.68	\$0.00241	2.4-4.8 g	\$5.79 to \$11.58	2.4 g	\$5.79
Pentasa	500mg tablets	\$120.61	\$0.00241	Up to 4 g	Up to \$9.65	2 g	\$4.82
	1 g tablets	\$135.30	\$0.00226		Up to \$9.02		\$4.51
	1 g granules	\$270.59	\$0.00225		Up to \$9.02		\$4.51
	2 g granules	\$254.36	\$0.00212		Up to \$8.48		\$4.24
	4 g granules	\$254.36	\$0.00212		Up to \$8.48		\$4.24
Salofalk	500mg tablets	\$120.61	\$0.00241	1.5-3 g	\$3.62 to \$7.24	1.5 g	\$3.62
	500mg granules	\$120.61	\$0.00241		\$3.62 to \$7.24		\$3.62
	1 g granules	\$225.49	\$0.00225		\$3.38 to \$6.76		\$3.38
	1.5 g granules	\$194.83	\$0.00216		\$3.25 to \$6.49		\$3.25
	3 g granules	\$194.83	\$0.00216		\$3.25 to \$6.49		\$3.25
Mesasal	250mg tablets	\$69.89	\$0.00280	1.5 g	\$4.19	0.75 g	\$2.10

Source: Constructed during evaluation based on Asacol, Mezavant, Pentasa, Salofalk and Mesasal Product Information, and Ex-manufacturer prices (excluding Efficient Funding of Chemotherapy) – 1 November 2016.

- 6.40 The effect of these differences in pricing is demonstrated when considering the wide range in price per year of maintenance treatment, from \$766.50 for Mesasal 0.75 g daily to \$2,113.35 for Mezavant and Asacol at 2.4 g daily. Given the other oral formulations are relevant comparators, the annual price cost-minimised price for Asacol could vary between \$1,857.12 to \$2,452.80 (using the lowest and highest price per mg of \$0.00212 and \$0.00280 respectively).
- 6.41 The PBAC has previously expressed uncertainty regarding the cost effectiveness of higher doses of mesalazine and has requested that the Department consider this in any future Post Market Review of colitis treatments (Mezavant PSD, November 2015).
- 6.42 The ESC noted that there is an upcoming DUSC review of medicines for the treatment of ulcerative colitis (DUSC Outcome Statement, September 2016).
- 6.43 The Pre-PBAC Response stated that the sponsor was willing to negotiate an appropriate price per milligram of mesalazine.

Drug cost/patient/month: from \$173.70 (2.4 g daily) up to \$347.40 (4.8 g daily) for induction of remission

- 6.44 Table 10 summarises the drug cost for Asacol based on the proposed ex-manufacturer price for induction of remission.

Table 10: Summary of drug cost for Asacol based on proposed ex-manufacturer price for induction

Brand	Strength and formulation	Pack	AEMP	Price per mg	Induction	
					Dose	Price per day
Asacol	800 mg tablets	90	\$173.68	\$0.00241	2.4-4.8 g	\$5.79 to \$11.58
Mezavant	1.2 g tablets	60	\$173.68	\$0.00241	2.4-4.8 g	\$5.79 to \$11.58

Source: constructed during evaluation

Abbreviation: AEMP, agreed ex-manufacturer price

- 6.45 The drug cost per patient per month for Asacol based on the proposed ex-manufacturer price of \$173.68 for a 90 pack was estimated to range from \$173.70 up to \$347.40 for induction of remission based on the recommended dose range of 2.4 g to 4.8 g per day. This is the same as the cost per patient per month for Mezavant.

Drug cost/patient/year: from \$1408.90 (1.6 g daily) up to \$2113.35 (2.4 g daily) for maintenance of remission

- 6.46 Table 11 summarises the drug cost for Asacol based on the proposed ex-manufacturer price for maintenance of remission.

Table 11: Summary of drug cost for Asacol based on proposed ex-manufacturer price for maintenance

Brand	Strength and formulation	Pack	AEMP	Price per mg	Maintenance	
					Dose	Price per day
Asacol	800 mg tablets	90	\$173.68	\$0.00241	1.6-2.4 g	\$3.86 to \$5.79
Mezavant	1.2 g tablets	60	\$173.68	\$0.00241	2.4 g	\$5.79

Source: constructed during evaluation

Abbreviation: AEMP, agreed ex-manufacturer price

- 6.47 The drug cost per patient per year for Asacol based on the proposed ex-manufacturer price of \$173.68 for a 90 pack was estimated to range from \$1,408.90 up to \$2,113.35 for maintenance of remission based on the recommended dose range of 1.6 g to 2.4 g per day. The ex-manufacturer price for Mezavant is \$173.68 for a 60 pack, with a drug cost per patient per year of \$2113.35 based on the recommended dose of 2.4 g daily for maintenance of remission.

Estimated PBS usage & financial implications

- 6.48 This submission was not considered by DUSC. To estimate the financial implications of the PBS listing of Asacol for the treatment of patients with ulcerative colitis, the submission assumed the number of patients likely to receive treatment with Asacol. The submission did not provide data to support these assumptions.

Table 12: Estimated use and financial implications

	Year 1 (Aug 2017 to Dec 2017)	Year 2 (2018)	Year 3 (2019)	Year 4 (2020)	Year 5 (2021)	Year 6 (2022)
Estimated extent of use						
Patients receiving Asacol	250	700	1,250	2,050	2,700	3,200
Asacol scripts ^{a, b}	575	3,222	5,754	9,436	12,429	14,729
Mezavant scripts ^{a, b, c}	589	3,300	5,893	9,665	12,729	15,086
Estimated net cost to PBS/RPBS (less patient co-payments)						
Total cost of Asacol	\$202,100	\$1,131,759	\$2,020,999	\$3,314,438	\$4,365,358	\$5,173,757
Total cost of Mezavant	\$206,673	\$1,157,368	\$2,066,728	\$3,389,435	\$4,464,133	\$5,290,825
Net cost to PBS/RPBS	-\$4,573	-\$25,609	-\$45,729	-\$74,997	-\$98,775	-\$117,068

Source: Tables 37-42, pp55-57 and 'Asacol Section D and E' Excel workbook of the submission

^a It was assumed that there were 50% less scripts in the first year due to August listing.

^b An adherence rate assumed to be 50% was applied.

^c Based on number of Asacol patients and assumed proportions receiving available Mezavant pack sizes (60 and 120 tablets)

- 6.49 At year 6, the estimated number of patients was 3,200. The cost savings of listing Asacol on the PBS/RPBS was estimated to be \$117,068 in the sixth year of listing; a cumulative saving over six years of \$366,751. The assumption that Mezavant 2.4 g could be substituted with Asacol 1.6 g resulting in a cost savings may not be reasonable given the lack of comparative efficacy data.
- 6.50 The estimated utilisation and financial implications were highly uncertain as the estimated utilisation of Asacol (based on total number of patients, scripts, adherence rate, dose splits) was based on assumptions that were inadequately justified or supported by clinical evidence.
- 6.51 The estimated number of Asacol prescriptions was most likely an underestimate of PBS utilisation, given the PBS utilisation of all oral formulations of mesalazine totalled 268,561 prescriptions from August 2015 to July 2016 (PBS item reports, Medicare Statistics).
- 6.52 The submission assumed that Mezavant would be the only treatment substituted by Asacol. Given that other, lower priced oral mesalazine formulations may also be substituted by Asacol, this assumption was unreasonable and most likely underestimated the cost of listing Asacol on the PBS.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

- 7.1 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 price per milligram of mesalazine.
- 7.2 The PBAC recommended that the wording of the restriction for the Asacol listing be consistent with that for the other oral mesalazine formulations for ulcerative colitis, with the inclusion of a note, "Not for the treatment of Crohn disease". The PBAC

recommended a maximum quantity of two packs (180 tablets), and five repeats.

- 7.3 In terms of the clinical place in therapy, the PBAC noted that the PSCR claimed Asacol 800 mg tablets offered flexibility in dose titration for patients compared with Mezavant 1.2 g tablets. The PBAC agreed with the ESC's advice that this claim had not been sufficiently substantiated given that a dose response was not demonstrated. Nonetheless, the PBAC did consider that the listing of an 800 mg tablet did allow for different of doses to be prescribed consistent with the TGA Product Information.
- 7.4 The PBAC noted that submission nominated Mezavant as the comparator and that the price per mg of mesalazine for Mezavant (\$0.00241) was higher than that for Pentasa tablets (\$0.00226-\$0.00241), Pentasa granules (\$0.00212-\$0.00225) and Salofalk granules (\$0.00216-\$0.00225).
- 7.5 The PBAC recalled that mesalazine granules were recommended for listing on the basis of the same price per mg compared to the tablets, and that Mezavant was recommended on a cost minimisation basis with Salofalk and Pentasa brands of mesalazine at the same price per mg of mesalazine. The PBAC considered all oral formulations of mesalazine to be alternative therapies and, as a significant improvement in efficacy or reduction in toxicity had not been demonstrated over any of the other oral formulations, the PBAC recommended Asacol be cost-minimised against the oral formulation of mesalazine with the lowest price per mg of mesalazine.
- 7.6 The PBAC considered that the claim of noninferior comparative effectiveness to Mezavant was uncertain but accepted it based on the totality of the evidence presented.
- 7.7 The PBAC considered that the claim of noninferior comparative safety to Mezavant was reasonable. Whilst limited detail was provided in the trial publications, the PBAC viewed that the safety profile of Asacol was consistent with the known safety profile of oral mesalazine.
- 7.8 The PBAC considered that the estimated utilisation and financial impact of the Asacol listing were insufficiently justified in the submission. The submission assumed that Mezavant would be the only treatment substituted by Asacol. The PBAC considered that other, lower priced oral mesalazine formulations may also be substituted by Asacol, and so the cost of listing Asacol was likely underestimated. The PBAC noted that listing Asacol on a cost-minimisation basis versus the lowest priced oral mesalazine formulation (on an equivalent mg to mg basis) should mitigate this.
- 7.9 The PBAC recommended that the Early Supply Rule should apply to Asacol, as it is applied to existing mesalazine oral formulations.
- 7.10 The PBAC advised that Asacol is suitable for prescribing by nurse practitioners as continuing therapy only.
- 7.11 The PBAC noted that this submission was not eligible for Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
MESALAZINE mesalazine 800 mg enteric tablet, 90	2	5	Asacol®	Baxter Australia

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Ulcerative colitis
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have had a documented hypersensitivity reaction to a sulphonamide, OR Patient must be intolerant to sulfasalazine.
Administrative Advice	Note Not for the treatment of Crohn disease Note Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.