

# The economics of mesalazine in active ulcerative colitis and maintenance in the Netherlands

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## ABSTRACT

**Background:** In this study we investigate the costs and benefits of topical mesalazine combined with oral mesalazine therapy for active ulcerative colitis (UC), and once daily (OD) mesalazine 2 grams versus twice daily (BID) for maintaining UC remission.

**Methods:** Two decision analytic models were constructed to evaluate treatment costs and quality-adjusted life years (QALYs) associated with mesalazine. The first model explored 4 g oral mesalazine in combination with 1 g topical mesalazine during active UC compared with 4 g oral mesalazine monotherapy for achieving clinical remission. The second model compared remission rates at one year for OD 2 g oral mesalazine compared with BID 1 g adjusted for compliance. All direct costs were obtained from established treatment costs in the Netherlands.

**Results:** The average cost of treatment to transition an active UC patient into remission using oral plus topical mesalazine or oral mesalazine monotherapy was €2207 (95% CI: €1402 to €3332) and €2945 (95% CI: €1717 to €4592), respectively. The annual average cost-saving of adding topical mesalazine delivered for four weeks during active UC was €738. The average annual costs of maintenance of remission with OD and BID therapy were €1293 (95% CI: €1062 to €1496) and €1502 (95% CI: €1262 to 1708), respectively with an annual average per person savings of €209.

**Conclusion:** Topical mesalazine during acute UC flares results in lower costs due to reduced healthcare consumption attributed to faster symptom resolution. Furthermore, as a result of lower costs and modest QALY gains, maintenance therapy using OD mesalazine is the dominant treatment option if compared with BID mesalazine.

## KEYWORDS

Mesalazine, cost-effectiveness analysis, ulcerative colitis, economic evaluation, maintenance therapy

## INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of the rectum and colon that is characterised by periods of remission with occasional, unpredictable episodes of relapse causing acute rectal bleeding, urgent diarrhoea and abdominal discomfort. Typically, the age of onset is between 20 to 40 years of age although the disease can be found in all age groups. Geographic variations have also been observed with 21 to 243 cases per 100,000, with 40% greater prevalence in Northern Europe compared with Southern Europe.<sup>1</sup> Additionally, previous studies have indicated that prevalence is increasing, therefore suggesting a need to understand disease aetiology and define cost-effective treatment practices to minimise the financial costs of care.<sup>2</sup> UC is a chronic condition that requires lifetime management. Because UC is lifelong, and often requires chronic therapy for maintaining remission,<sup>3</sup> defining cost-effective practices for this population is critical for optimising outcomes at low cost. However, because of the lifelong nature of UC, running long-term clinical trials to answer important research questions is not always feasible. Therefore, economic modelling is seen as a valid approach to fill gaps in our understanding of the costs and benefits of different therapies in the absence of long-term trials.<sup>4</sup> Treatment practices are increasingly influenced by cost-effectiveness in addition to medical benefits. In the Netherlands, since 2005, in addition to meeting efficacy, safety and quality standards, new medicines

must prove to be cost-effective compared with current treatment practices to obtain reimbursement under the Dutch system for medicines with proven added value.<sup>5</sup> Although cost-effectiveness standards were introduced formally at the national level in 2005, the practice of cost-effectiveness has been used since the 1980s for informing local formulary committees and treatment practices in the Netherlands.<sup>6</sup>

To inform treatment practices and formulary decisions in the Netherlands, we have developed two economic evaluations that explore the costs and consequences of mesalazine therapy in different situations. The first analysis compares the costs and benefits of adding topical mesalazine to treat mild-to-moderately active UC and the second evaluation compares the costs of OD 2 g with BID 1 g mesalazine for maintenance of remission. The models described here are based on a previously reported economic evaluation comparing OD and BID mesalazine dosing.<sup>7,8</sup> Although previous studies have reported the cost-effectiveness of these interventions, due to differences in treatments practice and costs in different countries it is often necessary to conduct country-specific economic analyses with local adaptations to test whether previous findings are valid.<sup>9</sup>

## METHODS

To assess the cost-effectiveness of mesalazine in active and quiescent UC, we adapted two previously described cost-effectiveness analyses. The model adaptation reflected both the differences in treatment practices and the costs of care in the Netherlands. Because the model frameworks have been previously described in detail,<sup>7,8</sup> we only discuss the relevant elements of the adaptations for the Netherlands in this publication.

### Research framework

The cost-effectiveness of introducing 1 g topical mesalazine at bedtime for four weeks in combination with 4 g oral mesalazine during active UC compared with 4 g oral mesalazine monotherapy was based on the randomised study reported by Marteau *et al.*<sup>10</sup> The study previously reported by Marteau observed remission rates of 64% (95% confidence interval 50% to 76%) and 43% (95% confidence interval 28% to 58%) that were significantly different for combined oral and enema therapy compared with oral monotherapy, respectively. The improved remission rates were achieved without any increase in adverse events.<sup>10</sup> These clinical differences served as the basis for economic modelling.

The economic evaluation in acute UC is based on the ability to achieve remission in mild to moderately active UC based on changes from baseline in the Ulcerative Colitis

Disease Activity Instrument (UCDAI).<sup>11</sup> The randomised study population considered in the analysis was >18 years of age with extensive UC and UCDAI scores  $\geq 3$  and  $\leq 8$ .<sup>10</sup> Five health states were considered in the active UC economic model: (1) combination therapy with oral mesalazine and topical mesalazine or oral mesalazine monotherapy; (2) mesalazine-refractory active UC; (3) steroid-refractory active UC; (4) infliximab-responsive active UC; and (5) remission. Following health state (1), the subsequent health states were comparable in both treatment arms.

### Maintenance of remission

In quiescent UC, we evaluated costs and outcomes of OD 2 g with BID 1 g dosing based on the randomised controlled study results reported by Dignass *et al.*<sup>12</sup> The main clinical outcome was remission defined as UCDAI scores  $\leq 1$ . The maintenance population recruited into the study were patients in UC remission (UCDAI <2), who had experienced a relapse requiring adjustments to their maintenance therapy within the past year. In the economic evaluation, UCDAI scores were converted into health state utilities based on two UC health states: (1) remission and (2) active UC treatment costs.

### Treatment practices in the Netherlands

In the Netherlands, usually a step-up regimen for treatment of active disease and maintenance of remission in UC is followed, according to national guidelines. In case of active UC, topical or oral mesalazine therapy, or a combination of both, is used depending on the extent and severity of the disease. The next step would be the addition of corticosteroids (topically and/or orally) and finally, if these fail as well, the initiation of rescue therapy (infliximab or cyclosporine). The first choice for maintenance therapy is mesalazine, typically in a dose of 2 to 4 g orally. In case of proctitis, mesalazine can be prescribed topically. Step-up includes thiopurines and, when these fail, infliximab.<sup>13-15</sup> The outcome measures included in the economic models are described in *table 1*.

### Resource utilisation items

The model was constructed from resource items in the Netherlands. The perspective applied in the analyses was the health service which included hospital and pharmacy costs. Resource use costs for consultation (e.g. specialist, general practitioner, IBD nurse) and follow-up visits were derived from the Dutch guideline for conducting costing research comprising of standardised prices.<sup>16</sup> Furthermore, unit costs for diagnosis (e.g. laboratory tests, endoscopy, X-ray), mesalazine and other treatments (e.g. beclometasone, prednisolone, Imuran, infliximab) were derived from official Dutch tariffs.<sup>17</sup> All costs were expressed in year-2010 values.

**Table 1.** Main outcomes included in model and variance applied in sensitivity analysis

Parameter	Point estimate	Variance	Reference
<b>Acute UC parameters and variance</b>			
Remission with 4 g oral mesalazine and 1g mesalazine enema*	0.64	(0.50-0.76)	10
Remission with 4 g oral mesalazine and placebo enema*	0.43	(0.28-0.58)	10
Probability success with prednisolone*	0.68	(0.43-0.87)	14
Probability success with infliximab*	0.39	(0.30-0.48)	15
<b>Maintenance therapy</b>			
OD 1-year relapse rate (95% CI)	0.738 <sup>†</sup>	(0.670-0.806)	12
BID 1-year relapse rate (95% CI)	0.636 <sup>†</sup>	(0.564-0.708)	12
Compliance OD <sup>‡</sup>	0.791	(0.593-0.989)	12
Compliance BID <sup>‡</sup>	0.798	(0.598-0.997)	12

<sup>†</sup>The difference in the primary outcomes was shown to be statistically significantly different based on Kaplan-Meier estimated UC-DAI remission rates at one year after randomisation; <sup>‡</sup>Compliance based on weighted compliance over entire study period with  $\pm 25\%$  variance applied. There was no significant difference between compliance rates; \*Based on reported outcomes at 8 weeks. BID = twice daily; OD = once daily.

Treatment costs for maintenance and active UC were estimated based on standard treatment practices in the Netherlands for managing acute UC events and applying Dutch tariffs to resources consumed. Annual drug costs were adjusted for mesalazine compliance rates reported for OD and BID maintenance therapy.<sup>12</sup>

**Modelled outcomes**

Ulcerative colitis is known to impact the quality of life of patients; therefore, the primary outcome of interest in the two economic models was the average QALY change based on the intention-to-treat populations from the randomised controlled trials. This is also the accepted outcome metric recommended by the Dutch authorities for making responsible budgetary and resource allocation decisions.<sup>18</sup> The QALYs were derived from previously reported UC health state utilities for remission and acute flares of 0.84 and 0.78, respectively,<sup>19</sup> and applied to the duration of time spent in each health state. Additional outcomes assessed in the model included the average cost of treatment over a defined period of time, costs per QALY and the incremental cost per QALY between different treatment options for active UC and maintenance. Because the time horizon considered in both models was less than one year, discount of costs and outcomes was not performed.

**Sensitivity analysis**

Variations in critical model parameters were evaluated using probabilistic sensitivity analysis (PSA). In the Netherlands, PSA, also referred to as second-order analysis, is recommended by the national body that evaluates

uncertainty around distributions for critical parameters where uncertainty may exist.<sup>18</sup> The point estimates and distributions assessed in the sensitivity for the maintenance and acute UC models are shown in *table 1*.

For each analysis, cost-effectiveness acceptability curves (CEAC) were generated using the net benefit approach to reflect uncertainty in the model. The CEAC output is useful for expressing the proportion of simulations in which one intervention is more cost-effective compared with the other across a range of willingness-to-pay (WTP) thresholds.<sup>20</sup>

**RESULTS**

**Active UC**

The average cost of treatment for a patient to transition from active UC to remission using oral mesalazine in combination with topical mesalazine or oral mesalazine monotherapy was estimated to be €2207 (95% CI: €1402 to €3332) and €2945 (95% CI: €1717 to €4592), respectively (*table 2*). This represents an average cost saving of €738 associated with topical mesalazine delivered for four weeks during active UC. The major cost difference between treatments occurred during steroid-refractory active UC as patients progressed to more expensive immunomodulating agents. A small incremental QALY increase of 0.01 was observed for patients treated with 1 g mesalazine enema compared with placebo-treated patients.

The average cost-effectiveness ratios for mesalazine enema and placebo enema were €3954 and €5345, respectively. The incremental analysis defined as  $(\text{Cost}_{4g \text{ oral} + 1g \text{ enema}} - \text{Cost}_{4g \text{ oral} + \text{placebo enema}}) / (\text{QALY}_{4g \text{ oral} + 1g \text{ enema}} - \text{QALY}_{4g \text{ oral} + \text{placebo enema}})$  indicated use of mesalazine enema to be the dominant treatment option in acute UC in the Netherlands (i.e. less costly and produces better outcomes).

**Table 2.** Average cost and QALYs for subjects treated with oral and topical mesalazine or oral mesalazine alone after 32 weeks of treatment<sup>‡</sup>

	4g oral mesalazine + 1g mesalazine enema	4g oral mesalazine + placebo enema
Average treatment costs	€2207	€2945
95% CI	(€1402-€3332)	(€1717-€4592)
Incremental treatment costs		(€738)
QALYs	0.56	0.55
95% CI	(0.55-0.57)	(0.54-0.56)
Incremental QALYs		0.01
Average cost-effectiveness ratios	€3954	€5345
95% CI	(€2491-€6023)	(€3089-€8468)
Incremental cost-effectiveness ratio	<b>Topical mesalazine dominant</b>	

<sup>‡</sup> Based on Monte Carlo simulation derived from 10,000 samplings.

The disaggregated assessment of costs indicated that topical mesalazine represented 2.2% (€49) of the total treatment costs. The costs of consultations and diagnostics represented 21% and 20% of total costs for topical mesalazine and placebo-treated subjects, respectively. The remainder of costs were attributed to aggressive pharmacological interventions used to treat patients refractory to mesalazine therapy in acute UC.

The model also generated cost-effectiveness acceptability curves over a range of different willingness to pay thresholds in the Netherlands ranging from €0 to €40,000 per QALY. The output suggests that over a range of willingness to pay thresholds, mesalazine enema has a greater than 95% chance of being cost-effective compared with no enema in active UC (figure 1).

### Maintenance

The average annual treatment costs for OD and BID therapy from the baseline model were €1293 (95% CI: €1062 to 1496) and €1502 (95% CI: €1262 to 1708), respectively with an annual average per person saving of €209 (table 3). The average annual mesalazine costs for OD (€700) and BID (€706) were similar, even after adjusting for differences in compliance rates. The average costs for treating relapse events with mesalazine OD and BID were €592 (95% CI: €467 to 730) and €795 (95% CI: €658 to 939), respectively. In addition to the annual cost-savings achieved with OD 2 g mesalazine, a small incremental QALY improvement of 0.004 was also observed, indicating OD was the dominant treatment option for maintaining remission.

**Table 3.** Base case average annual treatment costs and incremental cost-effectiveness ratios comparing 2g mesalazine OD and BID‡

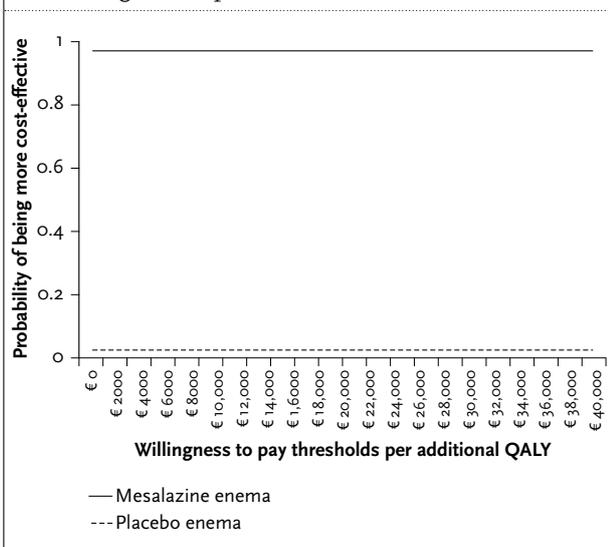
	Mesalazine 2g OD	Mesalazine 1g BID
Annual treatment costs‡ (95% CI)	€1293 (€1062-€1496)	€1502 (€1262-€1708)
Incremental cost per year (OD-BID)	(€209)	
QALYs (95% CI)	0.931 (0.928-0.933)	0.927 (0.924-0.929)
Incremental QALYs per year (OD-BID)	0.004	
Cost-effectiveness ratios (95% CI)	€1388 (€1265-€1502)	€1620 (€1362-€1847)
Incremental cost-effectiveness ratio	<b>2g OD dominant treatment option</b>	

‡ Based on Monte Carlo simulation derived from 10,000 samplings. BID = twice daily; OD = once daily. BID = twice daily; OD = once daily.

The disaggregated costs indicate mesalazine costs represent 54% and 47% of total costs for OD 2 g mesalazine and BID 1 g mesalazine-treated subjects, respectively. Ancillary costs of treating flares over the course of one year represented 46% and 53% of the costs for OD 2 g mesalazine and BID 1 g mesalazine-treated subjects, respectively.

Over the examined range of willingness to pay (WTP) thresholds from €0 to €40,000, mesalazine 2 g OD was found to deliver a higher proportion of benefits compared with mesalazine 1 g BID, with a 90% chance of being cost-effective for a WTP threshold per QALY of zero. As the WTP reached €40,000 per QALY, the likelihood that 2 g OD was more cost-effective was approximately 95% (data not shown). As health authorities would prefer to pay less per QALY this suggests 2 g OD represents a better treatment choice and in only 5% of cases 1 g BID would represent a more cost-effective option.

**Figure 1.** Cost-effectiveness acceptability curve comparing probability of being more cost-effective at different QALY willingness to pay thresholds for acute UC management options



### DISCUSSION

In the economic analysis of active UC we have shown that adding topical mesalazine offers cost savings for health services. The costs associated with returning a patient with mild to moderately active UC to remission in the Netherlands are approximately €2207 and €2945, respectively, for topical mesalazine compared with no topical mesalazine (placebo). This suggests an average saving of €738 per mild-to-moderately active UC patient treated. To achieve this result requires adding 1 g topical mesalazine for four weeks to 4 g oral mesalazine at a cost of approximately €49. The clinical effect size and resulting QALY differences described in the model are modest, suggesting the analysis is almost entirely influenced by avoiding the costs of treating the acute events.

The costs for returning a patient with active UC to remission are comparable with previous studies. In 2003 Bassi *et al.* reported six-month costs of patients experiencing an acute flare excluding hospitalisation to be  $\leq 765$  over a six-month period.<sup>21</sup> A more recent study in the United Kingdom reported 12-week costs associated with treating moderately active UC of  $\leq 2382$  per patient compared with  $\leq 2474$  dependent on whether first-line therapy of high dose (4.8 grams per day) or standard dose (2.4 grams per day) mesalazine was used.<sup>22</sup> However, in the study reported by Buckland, topical mesalazine was not considered in the analysis which may account for the small cost difference of  $\leq 92$ , in contrast with the cost differences reported in the analysis described here of  $\text{€}738$ .

The reduced costs and modest benefits of topical mesalazine are based on the ability to prevent progression to more expensive interventions used during acute events. Despite the benefits of topical mesalazine described here, and in head-to-head clinical trials,<sup>10</sup> there has been a downward trend in the utilisation of topical mesalazine during the period 1992 to 2009.<sup>23</sup> This downward trend in topical mesalazine use is concerning, considering the increasing incidence of UC and the likelihood of achieving downstream cost-savings is likely to be important for many local health authorities working with fixed budgets.<sup>24</sup>

One of the important aspects to this study is that health costs spent on pharmaceutical products such as topical mesalazine can save money for more expensive hospital-delivered care. This is an important message because funding silos within health services often means that budget holders only consider reimbursement decisions based on the impact within their own budget.<sup>6</sup> In the case of topical mesalazine, increasing pharmaceutical costs will save costs for treating acute events within hospital budgets. The maintenance of remission analysis described here highlights that OD 2 g mesalazine therapy is cost saving for maintaining UC remission compared with BID 1 g. The cost-effectiveness results described here likely represent an underestimate of mesalazine benefits because they do not include potential benefits in terms of occurrence of colorectal cancer (CRC) achieved with mesalazine therapy.<sup>25-27</sup> If the benefits associated with CRC prevention were included, then the costs of maintenance therapy would likely be lower from reduced resource use costs associated with treating CRC. Conversely, should mesalazine compliance in real-world settings be reduced and significantly more flares occur, the average cost-effectiveness ratios would increase.

The annual treatment costs for maintaining UC remission were  $\text{€}1293$  ( $\text{€}1062$  to  $\text{€}1496$ ) and  $\text{€}1502$  ( $\text{€}1262$  to  $\text{€}1708$ ) for OD and BID treatment practices. These annual treatment costs are broadly in line with previously reported European annual treatment costs for UC of  $\text{€}1524$ .<sup>28</sup> Furthermore, the effect size based on improved QALYs

between OD and BID mesalazine was only 0.004 QALYs between the two interventions. This highlights that the cost-effectiveness is influenced entirely by the costs associated with high-cost interventions used to treat acute UC events.

One of the limitations of our analysis is that we did not account for the indirect costs of the disease leading to lost productivity attributed to impaired health. In the case of UC, these costs may be substantial and could represent more than 50% of the total societal cost of UC.<sup>29</sup> However, due to limitations on working status in our clinical trial population we are unable to evaluate these costs in our analysis, although their inclusion in this analysis is not likely to influence the overall conclusions described in this paper because indirect costs normally follow direct costs, which were reported here.

Previous studies in the United States have suggested that maintenance therapy with mesalazine may not be justifiable, indicating the need to put the maintenance cost-effectiveness findings described here into perspective. In the study reported by Yen *et al.*,<sup>30</sup> the cost-effectiveness results were shown to be sensitive to the costs of mesalazine therapy and rate of flare reduction during maintenance therapy. In the study reported by Yen *et al.* the costs of mesalazine therapy are twice those in the Netherlands, which would likely influence the findings should a comparable study be conducted in the Netherlands. Furthermore, the analysis reported by Yen *et al.* also suggested a reduction in flare of 0.54 over a two-year period with maintenance therapy compared with no maintenance. Applying the rate of flare reduction reported by Yen *et al.* and factoring in the annual costs of maintenance therapy in the Netherlands, this would suggest a cost per flare avoided of  $\text{€}2593$ . The estimated cost per flare avoided is comparable with the costs associated with treating a flare, suggesting maintenance therapy may be cost-neutral in the Netherlands.

## CONCLUSIONS

In the Netherlands, and in many other countries, mesalazine is the cornerstone first-line therapy for maintaining remission and treating acute flares in mild-to-moderately active UC patients. Although daily treatment costs with mesalazine are relatively inexpensive, widespread acceptance and use of mesalazine suggests the budgetary impact could be important for guiding treatment practices and budgetary considerations. Because mesalazine is widely used we sought to establish the costs and consequences of its use in two clinical situations. The analysis described here indicates that the addition of 1 g topical mesalazine in combination with 4 g oral mesalazine is cost saving compared with oral monotherapy. The saving is achieved by

a moderate improvement in QALYs and reduced progression to more expensive interventions in those patients not responding to oral monotherapy. Furthermore, for maintenance of remission we established that OD 2 g is cost saving compared with BID 1 g. The saving with OD 2 g was achieved by reducing the number of people who experienced acute UC flares. It is envisaged that the findings reported here can be aligned with clinical guidelines to support the efficient use of healthcare resources in UC.

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