Summary form

# National Institute for Health and Care Excellence

## Multiple Technology Appraisal (MTA)

## Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262)

## Response to consultee and commentator comments on the draft scope

**Comment 1: the draft scope**

| Section | Consultees | Comments | Action |
|---|---|---|---|
| Background information | AbbVie | Yes *[response to question about accuracy and completeness of information]* | Comment noted |

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| | British Society of Gastroenterology | The epidemiological aspects are correct. The background includes aspects of the impact of ulcerative colitis on schooling, work relationships and quality of life in general; such aspects should be considered when looking at treatment outcomes, albeit that the published data may simply be 'quality of life'.<br>The disease being reviewed should be better defined. The MTA refers to moderately to severely active ulcerative colitis; the definitions of disease activity (page 1) moderately active UL adequately, but severe disease (as stated) defines acute severe disease: ie. patients who should be treated as in patients. There is an inconsistency between the patients to be address by this MTA and the BSG definitions.<br>The RCTs that underpin the product licenses are based on patients whose disease activity was defined using the Mayo scoring tool. This tool calls patients severe without the need for systemic features. Thus 'Mayo-severe' is not the same as 'BSG-severe'.<br>A better definition of the sick out-patient with UC is needed, that might define a 'severe' outpatient in a similar way to the Mayo score (but without the need to perform sigmoidoscopy.<br>A compromise might be to define moderate activity as per the BSG, a 'non-acute severe' as those patients having more than bloody bowel movements per day, but without tachycardia or fever. (Anaemia is not particularly useful in assessing severity in outpatients, unless it of new on-set).<br>When managing outpatients, azathioprine / methotrexate are used as steroid sparing agents; they are no used to induce remission. | Comment noted. Following discussion at the scoping workshop, the background section of the scope has been amended to clarify the population under consideration and the Truelove and Witts severity index has also been included. Broadly, people with acute severe ulcerative colitis with tachycardic and febrile symptoms are not included in the scope of this appraisal as guidance for this population is covered by TA163 and CG166. |
| | British Society of Paediatric Gastroenterology, Hepatology & Nutrition (BSPGHAN) | Accurate and correct | Comment noted |

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| | Crohn's and Colitis UK | It is important that the impact of UC on an individual's daily life is examined in the context of treatment outcomes and effectiveness. Particularly the ability to work and partake in education. | Comment noted |
| | Healthcare Improvement Scotland | Fine *[response to question about accuracy and completeness of information]* | Comment noted |

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| | Merck Sharp and Dohme | The penultimate paragraph states that: “NICE was unable to appraise adalimumab for treating subacute manifestations of moderately to severely active ulcerative colitis because the manufacturer did not provide an evidence submission (NICE technology appraisal guidance 262).” However, the scope for that appraisal specified that adalimumab would be appraised within the whole of its licensed indication; the scope did not limit the appraisal to only the subacute population.<br>The final paragraph states that: “a review of TA163 is not included in this appraisal, and so acute severely active ulcerative colitis is not included in this scope”. MSD feels that this statement contributes to a lack of clarity around the population being appraised; elsewhere in the draft scope the population is stated to be “people with moderately to severely active ulcerative colitis…” with no reference to the subacute or acute setting (table on page 3), Furthermore, the remit/appraisal objective (page 1) states that all technologies will be appraised “within their licensed indications for treating moderately to severely active ulcerative colitis | Comment noted. Attendees at the Scoping Workshop agreed that it was appropriate to exclude a review of TA163 from this appraisal and noted that TA163 would be reviewed when sufficient evidence became available and all technologies relevant to the acute severely active ulcerative colitis population would be taken into account. The background section of the scope has been amended to clarify the population under consideration and the Truelove and Witts severity index has also been included. Broadly, people with acute severe ulcerative colitis with tachycardic and febrile symptoms are not included in the scope of this appraisal as Guidance for this population is covered by TA163 and CG166. |
| | Primary Care Society For Gastroenterology | No comment | Response noted |

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| | Royal College of Nursing | Yes *[response to question about accuracy and completeness of information]* | Comment noted |
| The technology/ intervention | AbbVie | Yes *[response to question about the accuracy of the description of the technologies]* | Comment noted |
| | British Society of Gastroenterology | Yes *[response to question about the accuracy of the description of the technologies]* | Comment noted |
| | BSPGHAN | Appropriate *[response to question about the accuracy of the description of the technologies]* | Comment noted |
| | Celltrion Healthcare | Remsima (infliximab, Celltrion Healthcare) is developed as a similar biological medicial product to the medicinal product Remicade. The same indications for which Remicade is approved in the EU are approved for Remsima including adult and paediatric UC. | Comment noted. The 'technologies' section of the scope has been updated to reflect this. |
| | Crohn's and Colitis UK | We have no comments on this | Response noted |
| | Healthcare Improvement Scotland | Fine *[response to question about the accuracy of the description of the technologies]* | Comment noted |
| | Primary Care Society For Gastroenterology | Yes *[response to question about the accuracy of the description of the technologies]* | Comment noted |
| | Royal College of Nursing | We agree that the guidance does not take into account those who do respond. The greatest weight of evidence here is for infliximab. ACT studies report a response rate of 25% but subsequent real life experience in published data shows response and remission rates in the order of 70% (ref available). European guidance supports use of anti TNF - it is only in the UK that guidance goes against benefit of use. | Comment noted. The marketing authorisation for these interventions includes 'people…whose disease has responded inadequately' and so people who respond are not covered in this appraisal. |

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| Population | AbbVie | AbbVie considers that there are sub-groups within the moderate to severe UC population that could be considered separately e.g. patients who achieve a greater level of response/remission, or those patients for whom the risk of complications with either elective or urgent surgery is too great | Comment noted. Following discussion at the scoping workshop, it was agreed that, if evidence allows, patients with different durations of disease would be considered as separate subgroups. |

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| | British Society of Gastroenterology | No.<br>As mentioned above, the definition of severe active ulcerative used indicates acute severe disease which is outside the scope of this MTA.<br>Whilst immunosuppressants are used in maintenance and as steroid sparing drugs, there are not used to induce remission. In the context of this MTA, data should be stratified for immunosuppressant consumption. | Comment noted. Following discussion at the scoping workshop, the background section of the scope has been amended to clarify the population under consideration and the Truelove and Witts severity index has also been included. Broadly, people with acute severe ulcerative colitis with tachycardic and febrile symptoms are not included in the scope of this appraisal as guidance for this population is covered by TA163 and CG166. Following discussion at the scoping workshop, it was agreed that immunosuppressants should remain in the scope because of their role in maintenance as steroid sparing drugs. It was agreed that evidence would be separated into subgroups by the duration of disease. |
| | BSPGHAN | Yes *[response to question about the appropriateness of the definition of the population in the scope]* | Comment noted |
| | Crohn's and Colitis UK | We have no comments on this | Response noted |

| Section | Consultees | Comments | Action |
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| | Healthcare Improvement Scotland | Fine *[response to question about the appropriateness of the definition of the population in the scope]* | Comment noted |
| | Merck Sharp and Dohme | As stated in the previous comment, the population being appraised is described differently throughout the draft scope and consequently MSD do not feel that the population has been defined appropriately. In particular, MSD would like to seek clarity on whether the MTA is intended to review the remit of TA140 (entire population covered by the license indication for infliximab), or the recommendation of TA140 (subacute population only). | Comment noted. Following discussion at the scoping workshop, the background section of the scope has been amended to clarify the population under consideration and the Truelove and Witts severity index has also been included. Broadly, people with acute severe ulcerative colitis with tachycardic and febrile symptoms are not included in the scope of this appraisal as Guidance for this population is covered by TA163 and CG166. |
| | Primary Care Society For Gastroenterology | Yes *[response to question about the appropriateness of the definition of the population in the scope]* | Comment noted |

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| | Royal College of Nursing | The group that needs to be considered for treatment is those who are failing standard immunosuppressants and whose only options are continued poor quality of life and steroid-dependent disease or colectomy. Outpatients with sub-acute disease are often in a difficult situation as they have ongoing active disease that is often steroid dependant but who do not warrant admission. | Comment noted. The population is 'people with moderately to severely active ulcerative colitis whose disease has responded inadequately to conventional therapy…'. This does not exclude people who have had an inadequate response to immunosuppressants. |
| Comparators | AbbVie | Yes, the appropriate comparators have been listed. Given that treatment of acute exacerbations of severely active UC is not included within this scope, AbbVie considers that cyclosporine shouldn't be included as a comparator. | Comment noted. Following the discussions at the workshop, it was agreed that calcineurin inhibitors would be included as comparators. |
| | British Society of Gastroenterology | Yes; although the use of ciclosporin in outpatients might be added to the list of 'standard' therapies.<br>Best alternative care for outpatients with moderate-severe (Mayo) ulcerative colitis would be prolonged steroid therapy with the addition of immunosuppressants, in an attempt to sustain the remission brought about by the steroids.<br>The other alternative is elective surgery (colectomy with ileostomy). | Comment noted. Following the discussions at the workshop, it was agreed that calcineurin inhibitors would be included as comparators. |

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| | BSPGHAN | Design correct. We suggest that Ciclosporin and Tacrolimus should be included in the comparator while assessing the efficacy of IFX, ADA and Golimumab.<br>We suggest that now is the time to request evidence and to include Adalimumab for paediatric UC in the appraisal. Adalimumab is not authorised to market for this indication ( chronic UC ) in children. However it is very likely that this will get licensed in the near future for UC and data may be available on further request. We note your comments that "NICE was unable to appraise adalimumab for treating subacute manifestations of moderately to severely active ulcerative colitis because the manufacturer did not provide an evidence submission". However, we note that NICE included use of the drug beclomethasone for treatment of UC although we did not see clear evidence for use of this agent in UC | Comment noted. Following the discussions at the workshop, it was agreed that calcineurin inhibitors would be included as comparators. NICE can only issue guidance in line with marketing authorisation and therefore adalimumab has not been included as an intervention for children and adolescents. However, the scope allows for its inclusion as a comparator. |
| | Crohn's and Colitis UK | Tacrolimus as well as cyclosporine should be included as a comparator | Comment noted. Following the discussions at the workshop, it was agreed that calcineurin inhibitors would be included as comparators. |
| | Healthcare Improvement Scotland | Cyclosporin could be included as an additional comparator, though there is probably inadequate information about its use in this setting to achieve this. | Comment noted. Following the discussions at the workshop, it was agreed that calcineurin inhibitors would be included as comparators. |

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| | Merck Sharp and Dohme | - MSD kindly suggests that surgical intervention (elective or emergency) is not an appropriate comparator outside of the acute setting (and it is unclear whether this appraisal will consider that population).<br>- Section 1.3 of NICE Clinical Guideline 166 presents general information for patients considering surgery (not specific to a particular disease severity) but surgery is only recommended as a treatment option for patients with acute severe ulcerative colitis (sections 1.12.10 to 1.12.13 and 1.12.16 to 1.12.17). The guideline does not recommend surgery for mild to moderate ulcerative colitis and makes no recommendations for moderate to severe ulcerative colitis.<br>- Within all treatment settings, MSD believes that it is preferable for patients to receive effective treatment with approved biologics as an alternative to surgery or to prolong the time to surgery. | Comment noted. Attendees at the Scoping Workshop agreed that while many patients find treatment with biologics preferable to surgery, elective surgery should be included as a comparator as it is used in clinical practice in the UK for the population included in the appraisal. |
| | Primary Care Society For Gastroenterology | Yes and yes *[response to questions about whether the listed comparators are the standard treatments currently used in the NHS and whether they can be considered best alternative care]* | Comment noted |
| | Royal College of Nursing | Cya is not an appropriate therapy to consider in patients who have failed to respond to a thiopurine as it is a bridge to this therapy. The use of cya or infliximab salvage in the acute setting is covered by current guidance. Ciclosporin is generally only used in an inpatient setting and as a bridge to starting a thiopurine. | Comment noted. Following the discussions at the workshop, it was agreed that calcineurin inhibitors would be included as comparators. |
| Outcomes | AbbVie | Yes *[response to question about the appropriateness of the outcome measures]* | Comment noted |
| | British Society of Gastroenterology | Yes *[response to question about the appropriateness of the outcome measures]* | Comment noted |
| | BSPGHAN | Yes data collection should capture the benefits | Comment noted |

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| | Crohn's and Colitis UK | We have no comments on this | Response noted |
| | Merck Sharp and Dohme | "Rates of hospitalisation" is listed as an outcome for consideration; however, due to the lack of clarity around the population, it is unclear whether hospitalised patients (i.e. the acute setting) are to be considered within the appraisal.<br>MSD would like to note that for some of the specified outcomes data may be unavailable from randomised controlled trials. Rather, observational studies may be required to inform conclusions around mortality, rates of hospitalisation, and rates of surgical interventions (the latter outcome may also be provided through post-hoc RCT analysis). | Comment noted. Following discussion at the scoping workshop, the background section of the scope has been amended to clarify the population under consideration and the Truelove and Witts severity index has also been included. Broadly, people with acute severe ulcerative colitis with tachycardic and febrile symptoms are not included in the scope of this appraisal as guidance for this population is covered by TA163 and CG166. It was agreed that 'Rates of hospitalisation' is an appropriate outcome for this population. The Committee will assess the available evidence when making their recommendations. |
| | Primary Care Society For Gastroenterology | More could be explored in terms of primary care outcomes. For example, attendance at GP surgery, would a care pathway work in primary? | Comment noted. This question is outside of the remit of NICE technology appraisal guidance. |

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| | Royal College of Nursing | Steroid free remission also needs to be considered.<br>Mucosal healing on endoscopic assessment should be considered. | Comment noted. Following discussion at the scoping workshop it was agreed that steroid free remission is captured in the 'rates of and duration of response, relapse and remission' outcome. It was also decided not to include mucosal healing on endoscopic assessment as there are alternatives signs of treatment success that are less invasive and it is not routinely measured. |
| Economic analysis | AbbVie | No comments at present | Response noted |
| | British Society of Gastroenterology | The time horizon is not clear from the scope. I would recommend one year | Comment noted. The typical time horizon for most appraisals is a lifetime horizon, to be able to reflect any differences in costs and outcomes in the technologies being compared. The Committee will consider the most appropriate time horizon during the course of the appraisal. |
| | BSPGHAN | Satisfactory | Comment noted |
| | Crohn's and Colitis UK | We have no comments on this | Response noted |

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| | Primary Care Society For Gastroenterology | What are the economic benefits of providing this therapy in primary care?<br>At what cost would a CCG consider this treatment regime in the community? | Comment noted. These questions are outside of the remit of NICE technology appraisal guidance. |
| | Royal College of Nursing | Unable to comment | Response noted |
| Equality | AbbVie | None | Response noted |
| | British Society of Gastroenterology | Nil | Response noted |
| | BSPGHAN | None | Response noted |
| | Crohn's and Colitis UK | There is a need to give isoniazid as TB prophylaxis for 6 months in at risk patients, such as those from South Asia, concurrently with antiTNF therapy. | Comment noted. Following discussion at the scoping workshop, it was agreed that no changes to the scope were needed. Equalities issues will be considered by the Committee when formulating its recommendations. |
| | Primary Care Society For Gastroenterology | No comment | Response noted |

| Section | Consultees | Comments | Action |
|---|---|---|---|
| | Royal College of Nursing | Maintenance of remission needs to be considered, not just induction treatment. Currently, patients who have a good response must wait until they become unwell and hospitalised again before they can be re-treated with infliximab. This incurs additional costs from hospitalisation and distress to the patient.<br>Parameters need to be set outlining those patients who would be suitable to continue to maintenance and the duration of this. | Comment noted. |
| Other considerations | AbbVie | None | Response noted |
| | BSPGHAN | None | Response noted |
| | British Society of Gastroenterology | Vedolizumab is to be considered as a single technology for the same clinical indication. It would seem cost-effective and appropriate to add it to the current MTA. | Comment noted. It was discussed at the scoping workshop whether vedolizumab should be considered in the current MTA. However, given the timelines of an MTA, this could result in delaying the publication of guidance for vedolizumab. It was agreed based on the discussions at the scoping workshop that vedolizumab would be appraised in the single technology appraisal program to ensure timely guidance is issued. |

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|---|---|---|---|
| | Crohn's and Colitis UK | We recommend that vedolizumab is incorporated into this MTA given that it relates to UC as well | Comment noted. It was discussed at the scoping workshop whether vedolizumab should be considered in the current MTA. However, given the timelines of an MTA, this could result in delaying the publication of guidance for vedolizumab. It was agreed based on the discussions at the scoping workshop that vedolizumab would be appraised in the single technology appraisal program to ensure timely guidance is issued. |
| | Primary Care Society For Gastroenterology | Could this regime be delivered in primary care? | Comment noted. This is outside of the remit of this appraisal. |
| | ScHARR-TAG | Sequences of treatment may need to be considered and this should be included in the scope. | Comment noted. Based on discussions at the scoping workshop, it was agreed that the sequencing of drugs would not be included in the scope. |

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| Questions for consultation | AbbVie | AbbVie considers that adalimumab has the potential to make significant and substantial impact on patients' health related quality of life for example by reducing the rates of hospitalisation.<br>Adalimumab offers the opportunity of sub-cutaneous self-administration of the treatment at home following appropriate training with HCPs. AbbVie believes that this opportunity facilitates patient choice and as such is aligned with the NHS agenda to treat more patients closer to home.<br>The above mentioned long-term outcomes have been studied across the range of the controlled trials and the companion open-label extension. | Comment noted. Innovation will be considered by the Committee when formulating its recommendations. |
| | British Society of Gastroenterology | Yes – this will be a step change new therapeutic class. Given the lack of available therapies in this clinical scenario, it has the potential to impact substantially on management of refactory sub-acute UC.<br>Need to consider all the negative impacts of surgery – including poor pouch function / pouch failure / reduced fecundity. Also the long-term costs associated with pouch and/or stoma surgery<br>Phase II and III trial data. In addition, QoL data relating to pouch / stoma surgery | Comment noted. It was acknowledged at the scoping workshop that the negative impact of surgery will need to be taken into account in the appraisal. |
| | BSPGHAN | This is not a step change in the management of UC but further evidence in children is required to justify the changes in the care pathways that are developing. | Comment noted. |

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|---|---|---|---|
| | Crohn's and Colitis UK | It is important that the patient's views of surgery are taken into account, particularly the strong patient desire to avoid surgery and the significant psychological impact that stoma surgery can bring. | Comment noted. This was discussed at the scoping workshop in regards as to whether surgery is an appropriate comparator. Following the discussion, it was agreed that surgery is an appropriate comparator and that the negative impact of surgery will need to be taken into account by the Committee when making their recommendations. |

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|---|---|---|---|
| | Merck Sharp and Dohme | As stated previously, MSD do not believe surgery to be an appropriate comparator.<br>- MSD kindly suggests that ciclosporin should not be included as a comparator - evidence supporting its efficacy compared to standard of care is limited, it has not been shown to reduce colectomy, it has significant toxicities, food and drug interactions, a narrow therapeutic index, and slow onset of action in ulcerative colitis, supported by the ECCO guideline:<br>- The ECCO guideline (Dignass et al., 2012) states: “However, the narrow therapeutic index of ciclosporin and its side-effect profile (including mortality rates of 3-4%) have limited acceptability, such that in the 2008 UK National IBD audit only 24% of patients admitted with steroid-refractory severe UC received ciclosporin. A Cochrane review concluded that numbers in controlled trials were so few that there was limited evidence for ciclosporin being more effective than standard treatment alone for severe UC. Reluctance to use ciclosporin in this patient group may also reflect concerns about its ability to prevent colectomy in the longer term. In two series, 58% of 76 patients and 88% of 142 patients came to colectomy over 7 years. A single centre review of the long term outcome of 71 patients treated with iv ciclosporin for severe colitis reported that successful transition to an oral thiopurine was a significant factor in preventing future colectomy (OR 0.01, 95% CI 0.001-0.09, p<0.0001). Successful transition to thiopurine therapy and being thiopurine-naïve at baseline have been confirmed as factors that reduce the risk of long term colectomy in this patient group. Patients that have UC refractory to adequate thiopurine therapy may therefore be less suitable candidates for ciclosporin rescue therapy.”<br>- Further, ciclosporin is not licensed for the treatment of ulcerative colitis and is only recommended in NICE TA163 as an option for the treatment of acute severe ulcerative colitis (and it is unclear whether this appraisal will consider that population). | Comment noted. Following discussion at the workshop, it was agreed that surgery is a relevant comparator and that calcineurin inhibitors would be included as comparators. |

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| | Royal College of Nursing | This appraisal is overdue. This population of patients often suffer because they do not fit in either category of the current TA163 (fulminant uc) or TA140 - currently not recommended.<br>Patients are often unwell and steroid dependant/ refractory to conventional medication but the treatments that can be offered are limited unless they become unwell enough to be hospitalised. This hospitalisation could be avoided by earlier, appropriate use of Anti-TNF.<br>Cost benefits to be considered should include: Reduced hospitalisation, not just for potential surgery resulting from Fulminant UC, but also from admission for escalation of medical therapy to oral and IV corticosteroids. Also, the long term health costs of recurrent corticosteroids.<br>Data to be considered includes the ACT 1 AND 2 data, CONSTRUCT trial. It should be noted that data extrapolated from these studies do not always translate into the real world clinical setting. | Comment noted. This topic has been formally referred to NICE. The relevant costs, outcomes and data sources will be taken into account by the Assessment Group in their report and by the Committee when making their recommendations. |
| Additional comments on the draft scope. | BSPGHAN | BSPGHAN welcomes the scope | Comment noted |
| | ScHARR-TAG | There is likely to be a need to consider sequences of treatments and this may need to be mentioned in the scope. | Comment noted. Based on discussions at the scoping workshop, it was agreed that the sequencing of drugs would not be included in the scope. |

**The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope**

Department of Health

Pfizer