NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Use of tumour necrosis factor alpha (TNF α) inhibitors (adalimumab, certolizumab and infliximab [review]) and natalizumab for Crohn's disease

Responses to comments on the draft scope (Pre-referral)

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Schering Plough	Background information excludes mucosal healing which is an important clinical endpoint	Scope revised accordingly
	Elan Pharma	Elan endorses the background statement, with the exception of the statement that mortality is "slightly" increased. Recent European studies suggest that mortality is at least 1.3[1] and may be as high as 1.9[2] times higher than that of the general population. With 25-40% of deaths attributable to Crohn's[3]. The largest study to date was based on a sample from the UK GPRD database and suggested a mortality increase of around 70%, this study also had the advantage of addressing the risk to the "average" crohn's patient rather than incident cases[4]. Excess mortality may be yet higher in selected populations. We would suggest the alternative "significantly" in place of "slightly". 1) Jess T, Winther KV, Munkholm P, et al. Mortality and causes of death in Crohn's disease: follow-up of a population-based cohort in Copenhagen County, Denmark. Gastroenterology 2002;122:1808–14. 2) Wolters FL, Russel MG, Sijbrandij J, et al. Crohn's disease: increased mortality 10 years after diagnosis in a Europe-wide population based cohort. Gut 2006;55:510–8. 3) Loftus EV. Crohn's disease: why the disparity in mortality? *Gut.*2006; 55: 447-449 Card T, Hubbard R, Logan RF. Mortality in inflammatory bowel disease: a population-based cohort study. Gastroenterology 2003;125:1583–90.	Scope revised accordingly
	UCB	Short and comprehensive	Comment noted
	DHSSPSNI	Satisfactory	Comment noted

Section	Consultees	Comments	Action
	WMHTAC, University of Birmingham	You have included 'Tumour necrosis factor alpha (TNF-a) inhibitors (adalimimab, certolizumab and infliximab) and natalizumab may be used in some people with severe disease.' This suggests that all of these are already current treatments whereas three are not yet licensed, according to your scope, and are the subject of this appraisal.	The scope has been revised.
	NACC	In our view the range of prevalence is too wide and we would suggest should be close to the upper figure in the range quoted. Unless other comments support this view, then we would recommend that advice is taken from Professor Richard Logan (Nottingham) on this point to estimate a narrower range. Nutrition is also used as a therapeutic option in some centres and for some patients, particularly younger ones.	No other comments on the range received. No change. Comment noted
The technology/ intervention	Schering Plough	Infliximab's 2nd line licence is not captured in the background. In accordance with SPC infliximab is licensed for the management of severe active Crohn's disease in patients whose condition has not responded adequately to treatment with a corticosteroid **and/or** a conventional immunosuppressant or who are intolerant of them In accordance with SPC infliximab maintenance therapy is licensed for fistulising Crohn's disease. The licence does not restrict use of infliximab for refractory fistulising Crohn's patients	Scope revised accordingly
	Abbott Laboratories Ltd	It should be noted that infliximab is a chimeric antibody.	Scope revised accordingly
	Elan Pharma	- The commercial name for natalizumab should be changed from Antegren to Tysabri. The description of natalizumab should mention that it is currently licensed for the treatment of relapsing remitting multiple sclerosis (RRMS) in patients with high disease activity despite treatment with a beta-interferon or with rapidly evolving severe RRMS	Scope revised accordingly
	UCB	(Question) Yes	No action required
	DHSSPSNI	(Question) Accurate	No action required

Section	Consultees	Comments	Action
	WMHTAC, University of Birmingham	1. It is unclear why you have included three unlicensed drugs in this assessment. According to your scope only Infliximab is licensed 2. Current conventional treatment includes Infliximab so should be in the comparator only 3. It is unclear from the scope whether you are comparing the three new (unlicensed) drugs to current conventional treatment (ie clinical question is 'should we use the new ones or established conventional treatment') or whether you are comparing each new unlicensed treatment with each other (ie clinical question is 'which of the 3 new treatments should we use'). If you wish both clinical questions to be answered, this should be explicit in the scope. 4. It is unclear why you have singled out Natalizumab as it isn't a TNF alpha inhibitor. There are other drugs that could have been included such as CDP571 5. Are you interested in treatment in the acute phase or long term maintenance treatment, or both? 6. Maintenance therapy must be considered separately from induction of remission	1. The appraisal will consider include infliximab, natalizumab, adalimimab and certolizumab. However guidance will only be issued in accordance with the marketing authorisations for each of the technologies. 2. NICE has been requested to issue guidance will be issued on the use of infliximab for the treatment of Crohn's disease and is therefore included in the intervention section. 3. If the evidence allows the treatments will be compared to each other as well as conventional treatment. 4. CDP571 has not been referred to the Institute for appraisal and are therefore not included in the scope. 5. Will be considered within the marketing authorisation 6. Scope revised accordingly

Section	Consultees	Comments	Action
Population	Abbott Laboratories Ltd	The target population appropriately defines the patient population studied in the clinical trials of the biologic agents i.e. moderate to severe. However, guidance should be issued in accordance with the licensed indication for each agent with regard to patient severity. Given this background it would be useful to consider economic analyses in "moderate to severe" patients and "severe" patients separately. It will also be important to consider in a separate analysis, the subgroup of patients who have failed infliximab therapy.	Comments noted Guidance will be issued in accordance with marketing authorisation. Subgroups will be considered if clinically appropriate and if the evidence allows.
	Elan Pharma	[redacted]	If the evidence allows the treatments will be compared to each other as well as conventional treatment where appropriate
	UCB	Is the population defined appropriately? Yes. We may need a more critical definition of the population whether they have been previously exposed to biologics for this indication.	No action required
	Royal Pharmaceutical Society	Are there groups within this population that should be considered separately? People with refractory fistulating Crohn's disease intolerant of infliximab	The population reflects the current/anticipated licensed indications.
	DHSSPSNI	Defined appropriately. No other groups that should be considered separately.	No action required

Section	Consultees	Comments	Action
	WMHTAC, University of Birmingham	1. Infliximab is recommended for **severe** active Crohn's disease only (NICE guidance 40) yet your patient population in the scope is currently moderate to severe active Crohn's disease 2. How are you defining **moderate** Crohn's? Do you intend to use a standard CDAI/Harvey Bradshaw Index cut off point? 3. Therefore the target population is not yet adequately defined	The technologies will be appraised within their licensed indications. It is expected that moderate will be defined according to the inclusion criteria in clinical trials and the marketing authorisation
	NACC	We agree that the population is as defined – ie these interventions would not normally be used as first-line treatment - but we are concerned that the definition of 'not responded adequately' should not become the critical test for the use of the interventions in the sense that <u>all</u> other possibilities for conventional treatment have to have been tried in sequence and failed before the new interventions can be considered	The technologies will be appraised within their licensed indications.
Comparators	Abbott Laboratories Ltd	Infliximab is currently the most commonly used drug for the treatment of patients with severe Crohn's disease not responding to corticosteroids and/ or immunosuppressants or who are intolerant of these agents. As such, Abbott considers that the most appropriate comparator for adalimumab is currently infliximab. However, since most of the clinical trials of biologic agents in Crohn's disease have conventional therapy as the comparator, comparison versus conventional treatment strategies should also be considered.	Both are included in the scope.
	Elan Pharma	[redacted]	Comment noted
	UCB	The standard comparator should be the conventional treatments by non-biologics, as these are the routine treatments for this indication. By contrast, biologics are not currently routine treatment for this indication within the NHS.	This appraisal will compare all the treatments together if the evidence allows.

Section	Consultees	Comments	Action
	Royal Pharmaceutical Society	Include Methotrexate	Scope revised accordingly
	DHSSPSNI	Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Yes	No action required
	WMHTAC, University of Birmingham	1. Does the comparator include etanercept? Please list the TNF alpha inhibitors to be included as comparators.	Scope revised accordingly. Etanercept is not licensed for this indication
Outcomes	Schering Plough	Mucosal healing as an outcomes is not captured	Should be captured under disease activity
	Abbott Laboratories Ltd	It may be useful to also consider the potential benefits of therapy on other common comorbidities in persons with Crohn's disease. It may also be useful to consider patient preferences regarding drug administration.	Comments noted. These may be captured under health-related quality of life.

Section	Consultees	Comments	Action
	Elan Pharma	Elan endorses the proposed list of outcomes and recommends the inclusion of the following: - In the proposed indicated population for natalizumab very few non-surgical options remain, therefore potential to delay or avoid surgery and its associated morbidity and mortality should be considered - Because many of the treatments require the chronic co-administration of steroids or immunosuppressants which can have significant clinical impacts, estimates of the adverse effects of treatment with each of the evaluated therapies should make note of the rates of co-administration and the adverse effects of the co-administered products. - Because of the hazards of chronic steroid therapy, consideration should be given to analyses of the rates of steroid-free remission and steroid-free response as separate outcomes with each of the evaluated therapies. As CD affects the young and middle-aged, the disease results in demonstrable productivity losses and may affect the financial health of their families and their contributions to society. It is recommended that a sub-analysis of indirect costs be included in the evaluation.	Need for surgery included Adverse effects of treatment are included. The treatment of adverse events will be considered within the economic analysis. Adverse effects of treatment are included. The treatment of adverse events will be considered within the economic analysis. Costs should be from NHS perspective see methods guide 5.6.1.1
	UCB	Unlike cancer studies, survival and time-to-event data are not normally collected and analysed in the clinical studies of Crohn's disease. Proportion of remission and response based on CDAI or HBI are the primary end points in most of the trials on Crohn's disease. Withdrawal rate is an important outcome in trials of biologics which could reflect compliance issues, dosing and frequency, evidence of sustained remission.	Comments noted. It is expected that withdrawal from treatment will be reflected in disease activity, adverse effects and health-related quality of life.
	DHSSPSNI	Will these outcome measures capture the most important health related benefits of the technology? Yes	No action required

Section	Consultees	Comments	Action
	WMHTAC, University of Birmingham	1. What would be an adequate response to treatment in patients? How would this be defined? 2. Surgery is listed as a comparator and an outcome. How will you define the difference between the two?	The detail will be defined in the protocol The scope notes that surgery may be considered a part of conventional treatment strategies. If the interventions reduce the requirement for surgery this should be reflected in the economic analysis.
	NACC	Avoidance of surgery is a very important outcome for most patients and needs to be given due weighting in the analysis.	Included in outcomes
Economic analysis	Elan Pharma	- As CD is a lifetime disease, Elan proposes a lifetime horizon for economic modelling. - As CD affects the young and middle-aged, the disease results in demonstrable productivity losses and may affect the financial health of their families and their contributions to society. It is recommended that a sub-analysis of indirect costs be included in the evaluation. Elan endorses the consideration of different dosing schedules. Considerable dose escalation and/or shortening of the dosing interval have been noted for some of the evaluated therapies. The doses and dose frequency of the evaluated therapies should be based upon currently observed clinical practice (or estimated from currently approved indications, where necessary).	Comment noted Costs should be from NHS perspective see methods guide 5.6.1.1 Comment noted
	UCB	As Crohn's disease is a chronic disease, the timeframe for analysis should be medium to long for base case analysis.	No action required
	DHSSPSNI	10 years	No action required

Section	Consultees	Comments	Action
	WMHTAC, University of Birmingham	1. It is unclear from the scope whether you are comparing the three new (unlicensed) drugs to current conventional treatment (ie clinical question is 'should we use the new ones or established conventional treatment') or whether you are comparing each new unlicensed treatment with each other (ie clinical question is 'which of the 3 new treatments should we use'). If you wish both clinical questions to be answered, this should be explicit in the scope. This will involve two economic analyses rather than one. 2. In addition, the maintenance therapy question will also require a separate economic analysis. 3. Combining the moderate and severe indications into a single indication will have implications for the cost effectiveness analysis – the magnitude of health gain (even assuming a constant relative effect) is likely to be different in moderate and severe disease. This may lead to biased estimates of the population cost effectiveness of the treatment. It may be better to undertake separate cost effectiveness analyses for moderate and severe. This would leave open the possibility of different decisions. Does the Institute wish to pre-specify sub-group analyses for moderate Crohn's and severe Crohn's?	1. If the evidence allows the treatments will be compared to each other as well as conventional treatment. 2. Scope revised accordingly 3. The section 'Other considerations' notes that subgroups will be considered where the evidence allows.
Other considerations	Abbott Laboratories Ltd	Induction and maintenance of remission should be looked at in conjunction for the management of Crohn's disease.	Comment noted
	Elan Pharma	[redacted]	Scope revised accordingly to include different dosing schedules and the sequential use of treatments
Questions for consultation			

Section	Consultees	Comments	Action
Additional comments on the draft scope.	Abbott Laboratories Ltd	Abbott considers that patients, clinicians and those responsible for allocating funding for treatments for Crohn's disease would be best served by appraisal of adalimumab using NICE's STA process. Please correct spelling of "adalimimab" to "adalimumab" in the footer of the draft scope document.	It was considered a more logical course of action to review all potential Crohn's drugs in one appraisal
	Elan Pharma	[redacted] With respect to the question of whether induction and maintenance should be considered separately, it is Elan's view that the treatment strategy as a whole should be considered and not as separate induction and maintenance strategies. This is justified by both the trial design and the "real world" treatment paradigm, which is one of providing maintenance only to those who respond during induction and continue to benefit. Maintenance treatment can therefore not be considered as a separate strategy and withdrawing treatment post induction from those who are still receiving benefit would not represent good clinical practice.	No action required No action required Comment noted technology appraised according to marketing authorisation.
	UCB	As Crohn's disease usually starts at the age of 30-40 and is prevalent in young adults, productivity loss should be considered in the analyses and clinical studies have shown significant evidence of increased productivity with improvements in disease severity.	Costs should be from NHS perspective see methods guide 5.6.1.1
	NACC	In our view induction of remission may sometimes be the primary goal (eg. as preparation for surgery or because of some critical life event for the patient) but in most circumstances the aim will be to induce and maintain remission. Assuming the technology evaluation is not unfavourable, then the guidance should not limit the scope for the clinician and patient to decide which is the appropriate approach.	Comment noted

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Remit			
Current or proposed marketing authorisation	Abbott Laboratories Ltd	[redacted]	No action required
	Elan Pharma	[redacted] Tysabri (natalizumab) was approved for the treatment of relapsing remitting multiple sclerosis (RRMS) in patients with high disease activity despite treatment with a beta-interferon or with rapidly evolving severe RRMS in June2006.	No action required
	UCB	[redacted] The above responses are not yet in public domain, although previously indicated to NICE.	No action required

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

Wyeth
Department of Health
Welsh assembly government
Royal College of Physicians