National Institute for Health and Clinical Excellence

Abatacept for the treatment of juvenile idiopathic arthritis

Comment 1: the draft remit

Section	Consultees	Comments	Action
.Appropriateness	British Society of Paediatric and Adolescent Rheumatology (BSPAR)	Yes. The application of the existing Etanercept guidance has highlighted some of the practical difficulties, such as the exclusion of children under the age of 4 years. Therefore it is now highly appropriate to review the existing guidelines. Adalimumab is likely to receive a licence for the treatment of children with JIA in the very near future so a NICE judgement is well timed.	Comments noted. It was agreed at the scoping workshop that an appraisal of abatacept was appropriate. It was agreed at the scoping workshop that a review of the guidance for etanercept was not required. Adalimumab received a restricted licence for the treatment of JIA. For this reason it was removed from the technology appraisals work programme.
	Abbott Laboratories Ltd	Yes	Comment noted. It was agreed at the scoping workshop that an appraisal of abatacept was appropriate.
	Bristol-Myers Squibb Pharmaceuticals Ltd	It is appropriate for this topic to be referred to NICE for appraisal, provided that regulatory timelines are taken into account during scheduling of the appraisal.	Comment noted. It was agreed at the scoping workshop that an appraisal of abatacept was appropriate.

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	Arthritis Care	Arthritis Care welcomes the appraisal of abatacept for the treatment of juvenile idiopathic arthritis (JIA). At the moment there is a lack of licensed treatments for JIA. Without guidance, there is a risk that the benefits of abatacept will not be made available to young people across the UK who would derive considerable benefit from it- there is evidence that PCTs will not approve the use of anti-TNFs unless they are appraised by NICE. We therefore believe this appraisal to be timely and relevant.	Comments noted. It was agreed at the scoping workshop that an appraisal of abatacept was appropriate.
	Royal College of Paediatrics and Child Health (RCPCH)	Yes. The application of the existing Etanercept guidance has highlighted some of the practical difficulties, such as the exclusion of children under the age of 4 years. Therefore it is now highly appropriate to review the existing guidelines. Adalimumab is likely to receive a licence for the treatment of children with JIA in the very near future so a NICE judgement is well timed.	Comments noted. It was agreed at the scoping workshop that an appraisal of abatacept was appropriate. It was agreed at the scoping workshop that a review of the guidance for etanercept was not required. Adalimumab received a restricted licence for the treatment of JIA. For this reason it was removed from the technology appraisals work programme.
	Wyeth Pharmaceuticals	In the event that abatacept will receive marketing authorisation for juvenile idiopathic athritis it is appropriate to to refer this topic to NICE.	Comment noted. It was agreed at the scoping workshop that an appraisal of abatacept was appropriate.
Wording	BSPAR	Yes	Comment noted, no action required.
	Abbott Laboratories Ltd	Yes	Comment noted no action required.
	Bristol-Myers Squibb Pharmaceuticals Ltd	The wording of the remit reflects the issues that NICE should consider.	Comment noted no action required.

Section	Consultees	Comments	Action
	RCPCH	Yes	Comment noted, no action required.
	Wyeth Pharmaceuticals	Yes	Comment noted, no action required.
Timing Issues	Abbott Laboratories Ltd	Information on the suggested timing for the appraisal would be helpful at this stage.	Comment noted. Following the final referral from the Department of Health, the appraisal will be planned into the technology appraisal schedule to allow as timely as possible guidance to the NHS.
	Bristol-Myers Squibb Pharmaceuticals Ltd	Timing of the appraisal should appropriately reflect the licensing timelines.	Comment noted. Following the final referral from the Department of Health, the appraisal will be planned into the technology appraisal schedule to allow as timely as possible guidance to the NHS.
	Arthritis Care	Etanercept is currently the only anti-TNF drug licenced for children, and it will fail a proportion of them. We consider it a matter of urgency that alternative licenced treatments be made available.	Comments noted. Following the final referral from the Department of Health, the appraisal will be planned into the technology appraisal schedule to allow as timely as possible guidance to the NHS.
	Wyeth Pharmaceuticals	It is appropriate to appraise abatacept following its marketing authorisation.	Comment noted. Following the final referral from the Department of Health, the appraisal will be planned into the technology appraisal schedule to allow as timely as possible guidance to the NHS.

Section	Consultees	Comments	Action
Additional comments on the draft remit		No additional comments received	

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	BSPAR	Background para 2. The JIA subtypes should be described as follows: Systemic JIA, oligo arthritis (formerly pauciarticular), polyarthritis rheumatoid factor positive, polyarthritis rheumatoid factor negative, enthesitis related arthritis, psoriatic arthritis and unclassified. "Pauciarticular" should be replaced by oligo articular. Background para 4. Standard treatment for JIA includes the use of ***the disease modifying anti-rheumatic drug (DMARD), Methotrexate, alongside intra-articular and systemic corticosteroids and non-steroidal anti-inflammatory drugs (NSAID's).*** It is estimated that each year ***200 children*** (Ref BSPAR Biologics New Drugs Registry 2007) ***with JIA will start treatment with TNF inhibitors following the failure of Methotrexate treatment.***	Comments noted. The background section has been amended accordingly.
	Abbott Laboratories Ltd	Accurate and complete	Comment noted no action required.
	Bristol-Myers Squibb Pharmaceuticals Ltd	The background information is brief but accurate.	Comment noted no action required.

Section	Consultees	Comments	Action
	RCRePCH	Paragraph 2. The JIA subtypes should be described as follows: Systemic JIA, oligo arthritis (formerly pauciarticular), polyarthritis rheumatoid factor positive, polyarthritis rheumatoid factor negative, enthesitis related arthritis, psoriatic arthritis and unclassified. “Pauciarticular” should be replaced by oligo articular. Paragraph 4. We think this paragraph should be altered as follows: 'Standard treatment for JIA includes the use of the disease modifying anti-rheumatic drug (DMARD), Methotrexate, alongside intra-articular and systemic corticosteroids and non-steroidal anti-inflammatory drugs (NSAID’s). It is estimated that each year 200 children (Ref: BSPAR Biologics New Drugs Registry 2007) with JIA will start treatment with TNF inhibitors following the failure of Methotrexate treatment.'	Comments noted. The background section has been amended accordingly.
	Wyeth Pharmaceuticals	The information is accurate.	Comment noted no action required.
The technology/ intervention	BSPAR	Yes. It should be understood that although very similar the modes of action of Etanercept and Adalimumab are different. This explains why some patients respond to one anti-TNF alpha treatment better than another. It also explains why patients should be allowed a trial of a second anti-TNF alpha agent if therapy with the original anti-TNF agent was unsuccessful.	Comments noted. No actions required for the abatacept scope.
	Abbott Laboratories Ltd	Yes	Comment noted, no action required.
	Bristol-Myers Squibb Pharmaceuticals Ltd	The description of abatacept is not accurate. BMS suggests that "inhibits T cell proliferation" be replaced with "prevents T-cell activation by binding to CD80 and CD86 and inhibiting a co-stimulating signal.	Comment noted. The technology section has been amended accordingly.

Section	Consultees	Comments	Action
	RCPCH	Yes. It should be made clear that although very similar the modes of action of Etanercept and Adalimumab are different. This explains why some patients respond to one anti-TNF alpha treatment better than another. It also explains why patients should be allowed a trial of a second anti-TNF alpha agent if therapy with the original anti-TNF agent was unsuccessful.	Comments noted. No actions required for the abatacept scope.
	Wyeth Pharmaceuticals	Yes	Comment noted no action required.
Population	BSPAR	No. There should not be a lower age limit. It is inappropriate to exclude children under 4 years of age from the guidance. When patients move out of the paediatric or adolescent age group many will still need drug intervention therefore there should not be an upper age limit either. Perhaps we should discuss “patients” with JIA rather than “children”.	Comments noted. NICE can only make recommendations within the marketing authorisation of a technology. Therefore the guidance will cover the age groups that are included in the marketing authorisation.
	Bristol-Myers Squibb Pharmaceuticals Ltd	The population should include children and adolescents with JIA.	Comment noted. NICE can only make recommendations within the marketing authorisation of a technology. Therefore the guidance will cover the age groups that are included in the marketing authorisation. It was agreed at the scoping workshop that this would probably include both children and adolescents.

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	RCPCH	No. There should not be a lower age limit. It is inappropriate to exclude children under 4 years of age from the guidance. When patients move out of the paediatric or adolescent age group many will still need drug intervention therefore there should not be an upper age limit either. Perhaps we should discuss “patients” with JIA rather than “children”.	NICE can only make recommendations within the marketing authorisation of a technology. Therefore the guidance will cover the age groups that are included in the marketing authorisation.
	Wyeth Pharmaceuticals	Yes.	Comment noted. No action required.
Comparators	BSPAR	Methotrexate is the only DMARD (non anti-TNF) in routine use. Etanercept is currently the most widely used anti-TNF alpha drug and should be the main comparator. Infliximab (chimeric monoclonal antibody to TNF) is currently in wider use as the alternative to Etanercept, especially in children with JIA and uveitis. This may change pending reporting of efficacy and safety data of Adalimumab in JIA.	Comments noted. It was agreed at the scoping workshop that the comparators should include management strategies without the use of abatacept including conventional DMARDs and other alternative biologic DMARDs including adalimumab, etanercept and infliximab.
	Abbott Laboratories Ltd	The standard comparators listed are appropriate. It would be useful to consider to what extent etanercept is currently used in UK clinical practice for this patient population.	Comments noted. It was agreed at the scoping workshop that etanercept is currently the standard treatment for people for whom methotrexate has failed or is inappropriate.

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	Bristol-Myers Squibb Pharmaceuticals Ltd	At the moment, conventional DMARDs and etanercept are the only treatments licensed for use in JIA in the UK. BMS cannot comment on appropriateness of adalimumab and tocilizumab as comparators without information about the status of their respective license indications.	Comments noted. It was agreed at the scoping workshop that the comparators should include management strategies without the use of abatacept including conventional DMARDs and other alternative biologic DMARDs including adalimumab, etanercept and infliximab.
	Arthritis Care	We suggest the addition of infliximab as a comparator, as it is used where the patient develops uveitis as a complication of JIA.	Comments noted. It was agreed at the scoping workshop that the comparators should include management strategies without the use of abatacept including conventional DMARDs and other alternative biologic DMARDs including adalimumab, etanercept and infliximab. The other considerations section of the scope has been amended to include children with both JIA and uveitis, if the evidence and marketing authorisation allow.
	RCPCH	Methotrexate is the only DMARD (non anti-TNF) in routine use. Etanercept is currently the most widely used anti-TNF alpha drug and should be the main comparator. Infliximab (chimeric monoclonal antibody to TNF) is currently in wider use as the alternative to Etanercept, especially in children with JIA and uveitis. This may change pending reporting of efficacy and safety data of Adalimumab in JIA.	Comments noted. It was agreed at the scoping workshop that the comparators should include management strategies without the use of abatacept including conventional DMARDs and other alternative biologic DMARDs including adalimumab, etanercept and infliximab.

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	Wyeth Pharmaceuticals	The comparators are appropriate. However, in rheumatoid arthritis abatacept is recommended following the failure of at least 1 TNF.	Comments noted. It was agreed at the scoping workshop that the comparators should include management strategies without the use of abatacept including conventional DMARDs and other alternative biologic DMARDs including adalimumab, etanercept and infliximab.
Outcomes	BSPAR	Yes these are appropriate but the so called “core outcome variables” should also be used (ref Giannani et al Arthritis and Rheumatism 1997 (40); 1202).	Comments noted. The core outcome variables measure aspects of disease such as disease activity and physical function and will be addressed by the outcomes already listed.
	Abbott Laboratories Ltd	The impact of treatments on important comorbidities such as uveitis should be considered. Although outside NICE's reference case it may be useful to consider the benefits of successful treatment on the health related quality of life of parents in terms of factors such as anxiety.	Comments noted. The other considerations section of the scope has been amended to include children with both JIA and uveitis, if the evidence and marketing authorisation allow. Health related benefits to carers and parents are included in the NICE reference case.
	Bristol-Myers Squibb Pharmaceuticals Ltd	The outcomes listed will capture the most important benefits of the technology	Comment noted, no action required.

Section	Consultees	Comments	Action
	RCPCH	Yes, we think these are appropriate but the so-called “core outcome variables” should also be used (ref Giannani et al Arthritis and Rheumatism 1997 (40); 1202).	Comments noted. The core outcome variables measure aspects of disease such as disease activity and physical function and will be addressed by the outcomes already listed.
	Wyeth Pharmaceuticals	The outcomes should include quality adjusted life years, if not already covered by health related quality of life.	Comments noted. No outcomes were discussed at the scoping workshop that could not be covered by those listed in the draft scope.
Economic analysis	BSPAR	This is not my area of expertise. It seems likely that a number of patients with JIA will require treatment into adulthood. Economic analysis should take into account savings arising as a result of disease control eg less hospital visits for intra-articular injections and physiotherapy. If possible savings arising as a result of patients being independent and able to enter the workplace as adults rather than disabled and dependent on benefits should be considered. Timely intervention in childhood will reap lifetime benefit.	Comments noted. The NICE reference case states that the costs to be considered should be those arising from a NHS and PSS perspective. This would include savings to the NHS arising as a result of improved health related quality of life. The NICE reference case does not include productivity savings.
	Abbott Laboratories Ltd	Given the age of those suffering the condition it will be important to also consider the costs and outcomes of treatment from a societal perspective in sensitivity analyses. In particular, major elements may be the impact of successful treatment in minimising disruption to schooling and productivity costs for patients, parents and carers. Consideration should be given to whether costs are also incurred from the personal and social services perspective for these patients.	Comments noted. The NICE reference case states that the costs to be considered should be those arising from a NHS and PSS perspective. This would include savings to the NHS and PSS arising as a result of improved health related quality of life either for the individual child or the child’s parent/carer.

Section	Consultees	Comments	Action
	Bristol-Myers Squibb Pharmaceuticals Ltd	No comment	Comment noted, no action required.
	RCPCH	Although not our area of expertise we think it seems likely that a number of patients with JIA will require treatment into adulthood. Economic analysis should take into account savings arising as a result of disease control e.g. less hospital visits for intra-articular injections and physiotherapy. If possible savings arising as a result of patients being independent and able to enter the workplace as adults, rather than being disabled and dependent on benefits, should be considered. Furthermore, significant school loss may have long-term repercussions on these individuals employment prospects. There is data to support this for other chronic illnesses. Timely intervention in childhood will reap lifetime benefit.	Comments noted. The NICE reference case states that the costs to be considered should be those arising from a NHS and PSS perspective. This would include savings to the NHS arising as a result of improved health related quality of life. The NICE reference case does not include productivity savings.
	Wyeth Pharmaceuticals	The description of the economic analysis is appropriate.	Comment noted. No action required.
Equality Issues	BSPAR	I am not aware of equality issues on the grounds of race, disability, religion and sexual orientation in children in the UK. It will be important to avoid the “postcode prescribing” problems that have arisen with the Etanercept guidance. For example, the inequality of access of clinical nurse specialists to supervise the provision of Etanercept.	Comments noted. Where the licence stipulates that specialist provision is required, NICE cannot make recommendations outside of this.
	Bristol-Myers Squibb Pharmaceuticals Ltd	No comment	Comment noted. No action required.

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	RCPCH	We are not aware of equality issues on the grounds of race, disability, religion and sexual orientation in children in the UK. It will be important to avoid the "postcode prescribing" problems that have arisen with the Etanercept guidance. For example, the inequality of access to clinical nurse specialists to supervise the provision of Etanercept.	Comments noted. Where the licence stipulates that specialist provision is required, NICE cannot make recommendations outside of this.
	Wyeth Pharmaceuticals	Not applicable.	Comment noted. No action required.
	Abbott Laboratories Ltd	Equality may be an important factor in determining whether patients with juvenile arthritis have similar recommendations for use of biologic treatments compared to adults with rheumatoid arthritis.	Comment noted.
Other considerations	BSPAR	I would encourage the appraisal to consider the role of these therapies in the treatment of uveitis associated with JIA.	Comments noted. The other considerations section of the scope has been amended to include children with both JIA and uveitis, if the evidence and marketing authorisation allow.
	Arthritis Care	We note that the description of the effects of JIA does not mention its long term consequences. JIA persists into adulthood, and with inflammatory arthritis comes a risk of malignancy and a higher incidence of coronary artery disease and stroke. These factors, combined with the current lack of licenced treatments, mean that although a relativity rare condition, JIA has devastating effects throughout a person's life. We therefore consider the appraisal of medicines for use in combatting JIA to be extremely necessary and relevant.	Comments noted. The time horizon for the economic model would be expected to reflect the period over which costs and benefits would accrue. For JIA this would extend into adulthood and include costs and savings to the NHS and PSS during adulthood.
	Wyeth Pharmaceuticals	No	Comment noted. No action required.

Section	Consultees	Comments	Action
	RCPCH	We would encourage the appraisal to consider the role of these therapies in the treatment of uveitis associated with JIA.	Comment noted. The other considerations section of the scope has been amended to include children with both JIA and uveitis, if the evidence and marketing authorisation allow.
Questions for consultation	BSPAR	1. There is no definitive data that I am aware of relating to the duration of therapy in children. Many physicians will embark on trial of withdrawal after a prolonged period of control (eg 2 years) but practice varies. Significant proportion of those on treatment with Etanercept or Adalimumab will require continuation of treatment into adult life. There is some anecdotal evidence to suggest that patients may become "tolerant" to a given TNF alpha blocker after 2 or 3 years of treatment. A treatment break or switching to a different anti-TNF alpha agent may be indicated. 2. Recent epidemiological data suggests that between 35-60% of patients with JIA will still have active disease in adulthood. More severely affected patients are more likely to have persistent disease therefore many children will need anti-TNF alpha treatment in adult life. 3. JIA in combination with chronic anterior uveitis should be considered separately because their eye disease may be the primary indication for treatment with anti-TNF therapy rather than their joint disease. 4. Paediatric data on the use of anti-TNF alpha medication has been collected by the BSPAR Biologics and New Drugs Registry and this should be used as the primary source of data on the use of Etanercept rather than the British Society of Rheumatology Biologics Registry.	Comments noted. This information is useful and should be included in your submission for this appraisal. NICE can only make recommendations for a technology within the context of its marketing authorisation. The other considerations section of the scope has been amended to include children with both JIA and uveitis, if the evidence and marketing authorisation allow.
	Abbott Laboratories Ltd	Consideration should be given as to whether it is better to review all products for juvenile arthritis in an MTA.	It was agreed at the scoping workshop that a review of the guidance for etanercept was not required. Adalimumab received a restricted licence for the treatment of JIA. For this reason it was removed from the technology appraisals work programme.

Section	Consultees	Comments	Action
	Bristol-Myers Squibb Pharmaceuticals Ltd	Question 1: As stated above, conventional DMARDs and etanercept are the only treatments currently licensed for us in JIA in the UK. Given the uncertainty of the license status of adalimumab in JIA, precise wording of the abatacept license indication in JIA, and the goal of NICE guidance as close to launch as possible, BMS does not believe it would be appropriate to combine this appraisal with the proposed appraisal of adalimumab and etanercept in polyarticular juvenile idiopathic arthritis. Question 2 Treatment with abatacept for JIA is intended to be continuous, although intended or unintended dose interruptions may occur (e.g. due to remission, non-compliance, etc.). Period C of the BMS IM101-033 trial, is a continuous treatment phase. Question 3: Treatment with abatacept for JIA could continue into adulthood, based on decisions of individual physicians. Question 4: Given the small patient population, it is not possible to define sub-groups at this stage.	Comments noted. It was agreed at the scoping workshop that a review of the guidance for etanercept was not required. Adalimumab received a restricted licence for the treatment of JIA. For this reason it was removed from the technology appraisals work programme. Comments noted. This information is useful and should be included in your submission for this appraisal.

Section	Consultees	Comments	Action
	RCPCH	1. There is no definitive data that we are aware of relating to the duration of therapy in children. Many physicians will embark on trial of withdrawal after a prolonged period of control (eg 2 years) but practice varies. A significant proportion of those on treatment with Etanercept or Adalimumab will require continuation of treatment into adult life. There is some anecdotal evidence to suggest that patients may become “tolerant” to a given TNF alpha blocker after 2 or 3 years of treatment. A treatment break or switching to a different anti-TNF alpha agent may be indicated. 2.Recent epidemiological data suggests that between 35-60% of patients with JIA will still have active disease in adulthood. More severely affected patients are more likely to have persistent disease therefore many children will need anti-TNF alpha treatment in adult life. 3.JIA in combination with chronic anterior uveitis should be considered separately because the patient's eye disease may be the primary indication for treatment with anti-TNF therapy rather than their joint disease. 4.Paediatric data on the use of anti-TNF alpha medication has been collected by the BSPAR Biologics and New Drugs Registry and this should be used as the primary source of data on the use of Etanercept rather than the British Society of Rheumatology Biologics Registry	Comments noted. This information is useful and should be included in your submission for this appraisal. NICE can only make recommendations for a technology within the context of its marketing authorisation.

Section	Consultees	Comments	Action
	Wyeth Pharmaceuticals	The most appropriate comparators are mentioned in the comparator section above. Due to the differences between TNF inhibitors and and T cell proliferation inhibitors the appraisal of abatacept should not be combined with the one for adalimumab and etanercept. As there is administered on days 1, 15, and 29 of treatment and then every 28 days. It is supposed to be adminstered continuously during childhood. Due to the course of the disease, a categorisation into subgroups would not be appropriate.	Comments noted. It was agreed at the scoping workshop that a review of the guidance for etanercept was not required. Adalimumab received a restricted licence for the treatment of JIA. For this reason it was removed from the technology appraisals work programme. Comments noted. This information is useful and should be included in your submission for this appraisal.
Additional comments on the draft scope.	Department of Health	We understand that this is a new class of drug that will be considered for children, as it has the potential not only to treat arthritis but also to prevent/limit disability so very much in line with the NSF for children. We assume that this appraisal will be timed to co-ordinate with potential licensing of abatacept for children; if so, again in line with the NSF medicines for children. We feel that should this drug be significantly more expensive than other biologics for juvenile idiopathic arthritis, the economic analysis should compare with those as treatments *and* the lifetime cost benefit of reduced disability.	Comments noted. The other considerations section has been amended to include taking account of the benefits and costs associated with avoiding long-term disability, if the evidence allows.
	Rheumatoid Arthritis Surgical Society	As a surgical group we probably have little active input on this particular appraisal except to suggest that a view is taken about the continued use (or otherwise) prior to surgery and its continued use in the presence of active infection. The British Rheumatology Society have produced guidance on this (with which we do not totally agree but accept) but it should be a section in the HTA. A reduction in number of operations should not be used as an outcome as this could be achieved by making referral impossible	Comments noted.

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Remit		No comments received	
Current or proposed marketing authorisation	Bristol-Myers Squibb Pharmaceuticals Ltd	Abatacept in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other disease modifying anti rheumatic drugs including at least one tumour necrosis factor (TNF) inhibitor. A reduction in the progression of joint damage and improvement of physical function have been demonstrated during combination treatment with abatacept and methotrexate. CONFIDENTIAL: [redacted] CONFIDENTIAL: [redacted] EMEA centralised procedure CONFIDENTIAL: [redacted].	Comments noted.

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

Chartered Society of Physiotherapy
British Health Professionals in Rheumatology
Hospira UK
NHS Quality Improvement Scotland
NPHS Wales
Pfizer
Sanofi-Aventis