

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA 103 (part): Etanercept for the treatment of adults with psoriasis; TA 134: Infliximab for the treatment of psoriasis; TA 146: Adalimumab for the treatment of psoriasis and TA 180: Ustekinumab for the treatment of adults with moderate to severe psoriasis

This guidance was issued in July 2006 (TA103); January 2008 (TA134); June 2008 (TA146); September 2009 (TA180).

The review date for this guidance is “early 2010” (TAs 103, 134, 146); January 2010 (TA180)

Recommendation

- The appraisals should be moved to the static list.
- The appraisals should be incorporated, verbatim, within the ongoing clinical guideline on the *diagnosis and management of psoriasis in young people and adults*.
- We highlight that this proposal will have the consequence of preserving the funding direction.
- That we consult on the proposal.

Consideration of the recommendation

This review proposal has been prepared taking into account the principles outlined in the Department of Health policy document PWG IB (10)05 (see attachment). The process followed is outlined in the flow chart in Appendix 2.

Although there have been no significant new developments in the evidence base for these products that point to an update of the original technology appraisal, there is a relevant clinical guideline development. Therefore it is recommended that the technology appraisal guidance is incorporated, verbatim, into the clinical guideline.

If this proposal is agreed following consultation, the decision may need to be reviewed following scoping of the clinical guideline. In this instance a further consultation would be required.

It should be noted that TA180 includes an arrangement whereby the manufacturer provides the 90 mg dose (two 45 mg vials) for people who weigh more than 100 kg at the same total cost as for a single 45 mg vial. It would be necessary to confirm that this arrangement is not likely to change.

Below is a table summarising the consideration of review options:

Options	Comment
A review of the guidance should be planned into the appraisal work programme.	Although new evidence was uncovered, we do not believe this would warrant a departure from the Committee's original decision to recommend infliximab, etanercept, adalimumab and ustekinumab.
The decision to review the guidance should be deferred [to a specified date]	It is timely to consider incorporating them to the forthcoming clinical guideline
A review of the guidance should be combined with a review of a related technology and conducted at the scheduled time for the review of the related technology.	This review proposal covers all current relate technologies that NICE has previously appraised.
A review of the guidance should be combined with a new appraisal that has recently been referred to the Institute.	A related new appraisal (<i>ABT-874 for the treatment of moderate to severe chronic plaque psoriasis</i>) is in progress. However, we believe that that appraisal should still progress as an STA in order to ensure timely guidance.
These appraisals should be incorporated, verbatim, within the ongoing clinical guideline on the <i>diagnosis and management of psoriasis in young people and adults</i>.	There is a scheduled guideline on psoriasis which is currently at the pre-scoping stage. There is value in having a single resource to signpost clinicians to available NICE guidance on treatments for psoriasis. Given the absence of significant new evidence on these technologies, at present, we do not recommend that these appraisals are updated at present.
The guidance should be updated in an on-going clinical guideline.	We do not believe that a review at present would lead to substantial changes in the recommendations for these agents. If, during guideline scoping or development, it is proposed that the recommendations may have to be updated then a further consultation will need to take place.
A review of the guidance should be transferred to the 'static guidance list'.	It is timely to consider incorporating the appraisals within the forthcoming clinical guideline.

Original remit(s)

TA103/134: *“To appraise the clinical and cost effectiveness of alefacept, efalizumab, etanercept and infliximab within their licensed indications for the treatment of psoriasis; and if the evidence allows to give guidance on the selection of patients for whom treatment would be appropriate.”*

Note that, at the time of the original referral, efalizumab and etanercept were the only products licensed (and therefore appraisable by NICE). TA103 covered these two drugs. The portion of TA103 covering efalizumab has since been withdrawn following the withdrawal of its marketing authorisation. Efalizumab will therefore not be considered for review here. A single technology appraisal for infliximab (TA134) followed as licensing allowed.

TA146: *“To appraise the clinical and cost-effectiveness of adalimumab within its licensed indication for psoriasis.”*

TA180: *“To appraise the clinical and cost effectiveness of ustekinumab within its licensed indication for the treatment of moderate to severe psoriasis.”*

Current guidance

TA103

- 1.1 Etanercept, within its licensed indications, administered at a dose not exceeding 25 mg twice weekly is recommended for the treatment of adults with plaque psoriasis only when the following criteria are met.
 - The disease is severe as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more **and** a Dermatology Life Quality Index (DLQI) of more than 10.
 - The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant to, or has a contraindication to, these treatments.
- 1.2 Etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these patients. An adequate response is defined as either:
 - a 75% reduction in the PASI score from when treatment started (PASI 75) or...
 - a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from when treatment started.

1.3 Withdrawn

1.4 Withdrawn

1.5 It is recommended that the use of etanercept for psoriasis should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of psoriasis. If a person has both psoriasis and psoriatic arthritis their treatment should be managed by collaboration between a rheumatologist and a dermatologist.

1.6 Withdrawn

TA134

1.1 Infliximab, within its licensed indications, is recommended as a treatment option for adults with plaque psoriasis only when the following criteria are met.

- The disease is very severe as defined by a total Psoriasis Area Severity Index (PASI) of 20 or more and a Dermatology Life Quality Index (DLQI) of more than 18.
- The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate or PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant to or has a contraindication to these treatments.

1.2 Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to treatment within 10 weeks. An adequate response is defined as either:

- a 75% reduction in the PASI score from when treatment started (PASI 75) or
- a 50% reduction in the PASI score (PASI 50) and a five-point reduction in the DLQI from when treatment started.

1.3 When using the DLQI healthcare professionals should take care to ensure that they take account of a patient's disabilities (such as physical impairments) or linguistic or other communication difficulties, in reaching conclusions on the severity of plaque psoriasis. In such cases healthcare professionals should ensure that their use of the DLQI continues to be a sufficiently accurate measure. The same approach should apply in the context of a decision about whether to continue the use of the drug in accordance with section 1.2.

TA146

- 1.1 Adalimumab is recommended as a treatment option for adults with plaque psoriasis for whom anti-tumour necrosis factor (TNF) treatment is being considered and when the following criteria are both met.
- The disease is severe as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10.
 - The psoriasis has not responded to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant of, or has a contraindication to, these treatments.
- 1.2 Adalimumab should be discontinued in people whose psoriasis has not responded adequately at 16 weeks. An adequate response is defined as either:
- a 75% reduction in the PASI score (PASI 75) from when treatment started, or...
 - a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from start of treatment.
- 1.3 When using the DLQI, healthcare professionals should ensure that when reaching conclusions on the severity of plaque psoriasis they take into account a person's disabilities (such as physical impairments) and linguistic or other communication difficulties. In such cases, healthcare professionals should ensure that their use of the DLQI continues to be a sufficiently accurate measure. The same approach should apply in the context of a decision about whether to continue the use of adalimumab in accordance with section 1.2.

TA180

- 1.1 Ustekinumab is recommended as a treatment option for adults with plaque psoriasis when the following criteria are met.
- The disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) score of 10 or more **and** a Dermatology Life Quality Index (DLQI) score of more than 10.
 - The psoriasis has not responded to standard systemic therapies, including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant of or has a contraindication to these treatments.

- The manufacturer provides the 90 mg dose (two 45 mg vials) for people who weigh more than 100 kg at the same total cost as for a single 45 mg vial.
- 1.2 Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment. An adequate response is defined as either:
- a 75% reduction in the PASI score (PASI 75) from when treatment started **or**
 - a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in the DLQI score from when treatment started.
- 1.3 When using the DLQI, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the DLQI and make any adjustments they consider appropriate.

Relevant Institute work

Published

Adalimumab for the treatment of psoriatic arthritis. Technology Appraisal TA125. Issued: August 2007.

Etanercept and infliximab for the treatment of psoriatic arthritis. Technology Appraisal TA104. Issued: July 2006.

Grenz rays therapy for inflammatory skin conditions. Interventional Procedure Guidance IPG 236. Issued: November 2007

In progress

Diagnosis and management of psoriasis in young people and adults. Clinical Guideline. Expected issue date: January 2013.

ABT-874 for the treatment of moderate to severe chronic plaque psoriasis. (Single) Technology Appraisal. Expected issue date: December 2011.

Etanercept, infliximab, and adalimumab for the treatment of psoriatic arthritis (review). Expected issue date: July 2010.

Suspended or terminated

Psoriatic arthritis (moderate to severe) - leflunomide (suspended)

In topic selection



Safety information

The US FDA reported concerns on the use of use of etanercept in children in 2008 (source: NELM), however a license extension covering paediatric plaque psoriasis was subsequently granted by the EMEA.

Details of new indications

Drug (manufacturer)	Details
Etanercept (Pfizer (formerly Wyeth))	License extension for chronic, severe plaque psoriasis in children aged 8+ granted by the EMEA in January 2009.
Infliximab	None relevant to this appraisal
Adalimumab	None relevant to this appraisal
Ustekinumab	None relevant to this appraisal

Details of new products

Drug (manufacturer)	Details
Apremilast (Celgene)	Phase II UK launch planned Q1 2011
BG 12 (Biogen)	Phase III
Briakinumab (ABT-874) (Abbott)	Phase III Already on NICE work programme (see above).
Voclosporin (Lux Biosciences)	Phase III UK launch planned Q1 2012

On-going trials

Trial name	Details
Moderate to Severe Plaque Psoriasis With Scalp Involvement	Phase IV Estimated primary completion date: November 2009
Study Comparing 2 Different Strategies For Management of Subjects With Plaque Psoriasis Who Have Responded to Etanercept	Phase IV Estimated primary completion date: January 2012
Evaluation of Etanercept in Patients With Plaque Psoriasis After Stopping Ciclosporin Therapy	Phase IV Estimated primary completion date: December 2007
Study Evaluating the Efficacy and Safety of Etanercept and Acitretin in Korean Patient With Moderate to Severe Psoriasis	Phase IV Estimated primary completion date: October 2010

Trial name	Details
A Long Term Safety Study of Infliximab (Remicade)	Follow up (\leq 5 years) of participants from previous infliximab studies. Estimated completion date: not stated
The Influence of Adalimumab on Cardiovascular and Metabolic Risk in Psoriasis	Phase IV Estimated primary completion date: May 2013
Effect of Adalimumab on Vascular Inflammation in Patients With Moderate to Severe Plaque Psoriasis	Phase IV Estimated primary completion date: August 2010
A Study of the Safety and Effectiveness of Ustekinumab (Stelara) in Chinese Patients With Psoriasis	Phase III Estimated completion date: January 2011
A Phase 3 Trial to Look at the Safety and Effectiveness of Ustekinumab in Korean and Taiwanese Subjects With Moderate to Severe Plaque-type Psoriasis	Phase III Estimated primary completion date: October 2009
A Study of the Safety and Efficacy of Ustekinumab in Adolescent Patients With Psoriasis (CADMUS)	Phase III Estimated completion date: June 2013
A Study of the Safety and Efficacy of Ustekinumab in Patients With Psoriatic Arthritis Who Have Prior Exposure to Anti TNF Agents	Phase III Estimated primary completion date: April 2011

Proposed Timing for updating the guidance

If the guidance was updated as a technology appraisal it would be scheduled into the work programme accordingly.

New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from the dates of the original searches onwards were reviewed. The results of the literature search are discussed in the 'Appraisals comment' section below.

Implementation

A submission from Implementation is attached at the end of this paper (Appendix 1).

Equality and diversity issues

No relevant equality and diversity issues have been identified.

Appraisals comment:

No new RCTs which assess the efficacy of infliximab compared to placebo in adults with psoriasis have been published since the appraisal.

Three new RCT which assesses the efficacy of etanercept compared to placebo in adults with moderate to severe psoriasis have been published since the appraisal. All the studies identified a statistically significant difference in favour of etanercept 25 mg over placebo as measured by PASI 75 at 12 weeks.

A pooled analysis of 3 RCTs comparing adalimumab (40mg every other week) with placebo in adults with psoriasis has been published since the appraisal. The study identified a mean percentage PASI improvement of 78.3% for adalimumab vs. 15.1% for placebo at 16 weeks.

A systematic review published since the appraisal concluded that ustekinumab, reduces the extent and severity of psoriasis and was well tolerated in clinical trials.

The manufacturers did not provide details of any other published RCTs or systematic reviews

Studies comparing systemic treatments for moderate to severe psoriasis

An RCT comparing etanercept with ustekinumab has been published since the appraisal. The study found that the efficacy of ustekinumab at a dose of 45 or 90 mg was superior to that of high-dose etanercept over a 12-week period in patients with psoriasis. The results of this study for the PASI 75 score are identical to those presented in the TA180 FAD indicating that this publication may relate to a study that was included in the submission.

Three mixed treatment comparison analyses comparing systemic treatments for moderate to severe psoriasis have been published since the appraisal(s). In one study adalimumab and infliximab were found to be more effective than etanercept. Another study found that the treatments with the greatest efficacy were infliximab, and then etanercept, when compared with placebo. A third study comparing the safety of systemic treatments for moderate and severe psoriasis found there were no significant differences between TNF-alpha inhibitors and placebo in the proportions of patients experiencing withdrawal for any reason (RR 0.48, 95% CI 0.20-1.18), or withdrawal due to adverse events (RR 2.14, 95% CI 0.73-6.27), serious adverse events (RR 0.98, 95% CI 0.55-1.77), or upper respiratory tract infections (RR 0.91, 95% CI 0.65-1.28).

There is no new evidence to warrant a departure from the Committee's original decision to recommend infliximab, etanercept, adalimumab and ustekinumab for the treatment of psoriasis. There is now some evidence on which to base decisions on to where in the treatment pathway each of these treatments should be considered.

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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

IMPLEMENTATION DIRECTORATE

Guidance Executive Review

Technology appraisal 103 (part): Etanercept for the treatment of adults with psoriasis; technology appraisal 134: Infliximab for the treatment of psoriasis; technology appraisal 146: Psoriasis – adalimumab and technology appraisal 180: Ustekinumab for the treatment of adults with moderate to severe psoriasis

1. National Prescribing

1.1 Hospitals

Data showing trends in prescribing costs and volume are presented below. Unfortunately this data does not link to diagnosis so needs to be treated cautiously in relation to the specific recommendations of the guidance. Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Figure 1 Trend in volume of prescribing etanercept, infliximab and adalimumab in hospitals in England

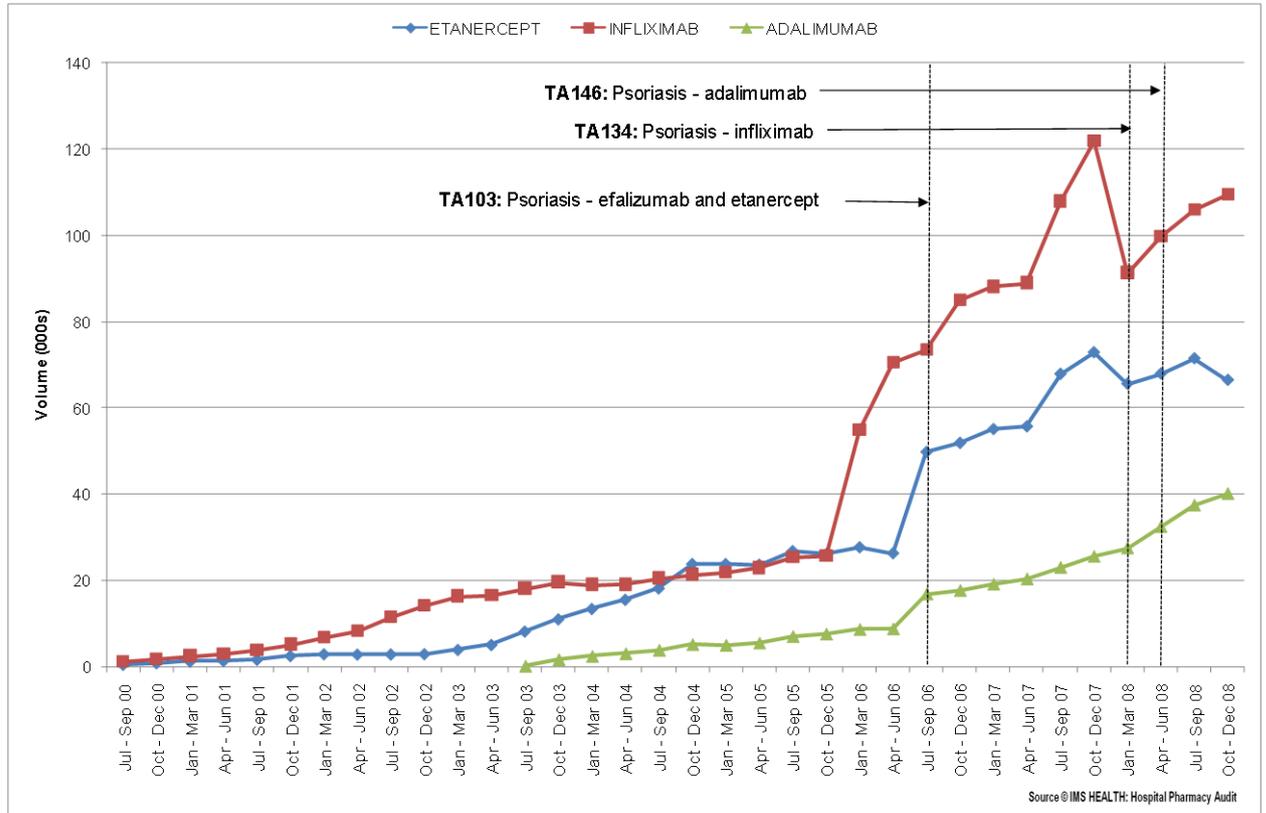
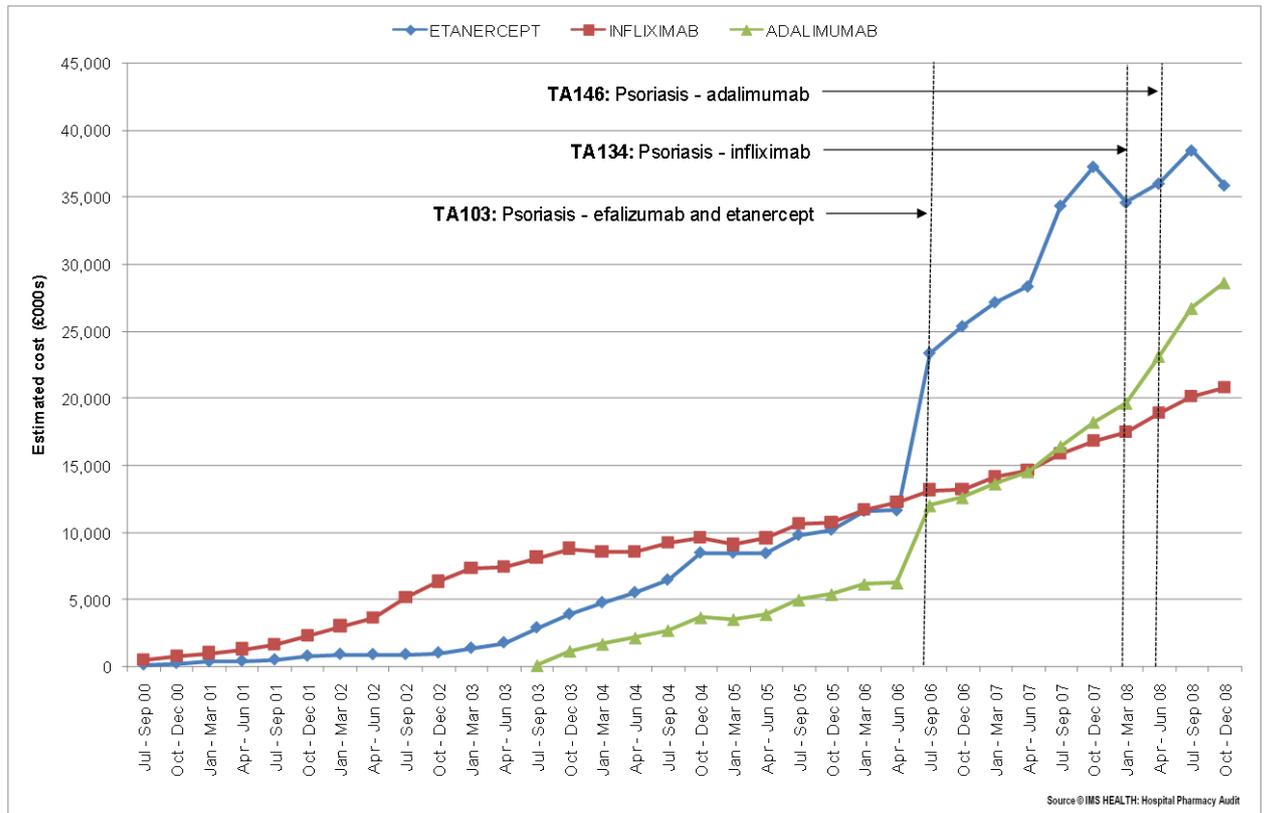


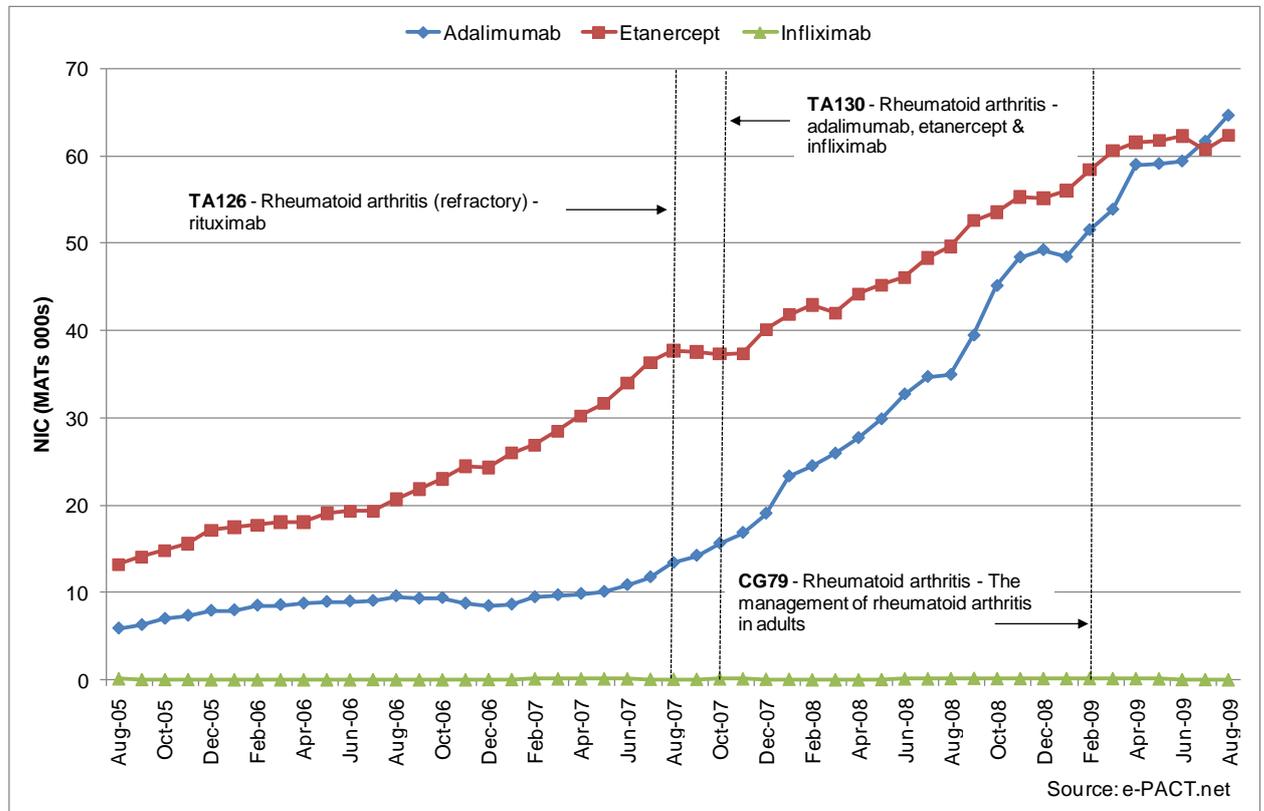
Figure 2 Trend in cost of prescribing etanercept, infliximab and adalimumab in hospitals in England



1.2 Primary care

This section provides information on prescribing cost for etanercept, infliximab and adalimumab in primary care in England. The data are obtained from the electronic Prescribing Analysis Cost Tool (ePACT) system which is maintained by the Prescription Services Division of the NHS Business Services Authority (BSA). All costs stated in this report are based on net ingredient cost (NIC).

Figure 3 Total Net Ingredient Cost (NIC) for adalimumab, etanercept and infliximab prescribed and dispensed in primary care in England.



2. External literature

2.1 ERNIE

2.1.1 The Information Centre for Health and Social Care (2009) Hospital Prescribing, 2008: England

http://www.ic.nhs.uk/webfiles/publications/Primary%20Care/Prescriptions/hospre08/Hospital_prescribing_2008_report2.pdf

Cost (£000s)	Primary care	% growth primary	FP10HP *	% growth	Hospital	% growth hospital	Total	% growth total
Etanercept	662.3	37.5	6,374.9	39.3	145,138.6	14.0	152,175.7	15.0
Infliximab	2.1	66.7	-	-	77,131.0	25.3	77,133.1	25.3
Adalimumab	591.3	158.4	3,964.0	26.1	98,175.6	56.2	102,730.9	55.1

*FP10HP = prescriptions written in hospitals but dispensed in the community



The data shows that the majority of prescribing for etanercept, infliximab and adalimumab is carried out in a hospital setting.

Illustration of the decision process for considering review proposals in the context of a clinical guideline

