TA 187: REQUEST FOR FUNDING OF ADALIMUMAB OR (INFLIXIMAB) FOR CROHN’S DISEASE IN ADULTS

Drugs covered by this Group Prior Approval arrangement: Adalimumab and Infliximab (anti TNFs). For the purposes of this group prior approval these drugs will be regarded as “standard biologic treatments”.

This form to be used to notify the patient’s CCG of treatment initiation OR temporary interval shortening OR to apply for prior approval of dose escalation.

East of England CCGs will not normally fund any Crohn’s patient’s anti-TNF treatment where the patient does not meet the agreed criteria as outlined in this Group Prior Approval. If the consultant gastroenterologist wishes to treat with anti-TNF therapy outside the terms of this GPA, the funding for the therapy would have to be borne from within the Trust’s existing drug budget, subject to local hospital approval mechanisms.

Please ensure this form is countersigned by Trust Chief Pharmacist (or deputy) before onward transmission to CCG.

Only fully completed forms will be accepted for consideration by the CCGs.

If the answer to any of these questions is NO, then a full Individual Funding Request form will need to be completed and these may be obtained from the relevant Individual Funding Co-ordinator.

Bedfordshire Clinical Commissioning Group (BCCG): e-mail (Preferred method): Beds.IFRrequests@nhs.net or telephone 01494 555530. IFR team, South, Central and West CSU, Albert House, Queen Victoria Road, High Wycombe, HP11 1AG.

Luton Clinical Commissioning Group (LCCG): luton.itp@nhs.net; Secure fax: 01582 511054, The Lodge, 4 George St West, Luton, Beds, LU1 2BJ

Payment by the CCG will only be made if the completed form is received no later than 15 days after INITIAL treatment commences and must be received and authorised BEFORE dose escalation.

On-going funding is requisite to the commissioner receiving a completed copy of the monitoring sheet (page 5) at 12 weeks, 6 months, 12 months and then after every 12 months.
<table>
<thead>
<tr>
<th>Patient NHS No.</th>
<th>Trust:</th>
<th>GP Name:</th>
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</thead>
<tbody>
<tr>
<td>Patient Hospital Number:</td>
<td>Consultant Making Request:</td>
<td>GP code / Practice code:</td>
</tr>
<tr>
<td>Patient initials &amp; DoB:</td>
<td>Consultant Contact Details:</td>
<td>GP Post code:</td>
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</table>

**Patient Criteria for Starting Treatment**
For the purposes of funding all definitions are those set out in the NICE TAG 187 which sets out the recommendations on use of these treatments.

<table>
<thead>
<tr>
<th>Patient has the following diagnosis</th>
<th>Please advise of any deviation from the patient criteria and rationale for proposing treatment with these drugs despite this deviation from the GPA:</th>
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<tbody>
<tr>
<td>adult with severe active Crohn’s disease</td>
<td>Severe active Crohn’s disease is defined (TA187) as 1. Very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. People with severe active Crohn’s disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally, but not exclusively, corresponds to a Crohn’s Disease Activity Index (CDAI) score of 300 or more, or a Harvey-Bradshaw score of 8 to 9 or above <strong>AND</strong> 2. Patients whose disease has not responded to maximum tolerated doses of conventional therapy (including immunosuppressive and/or corticosteroid treatments) given for an adequate period or who are intolerant of or have contraindications to conventional therapy</td>
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<tr>
<td>adult with fistulating Crohn’s disease</td>
<td>Active fistulising Crohn’s disease is defined (TA187) as Disease that has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or where the patient is intolerant of or has contraindications to conventional therapy.</td>
</tr>
</tbody>
</table>

**Harvey Bradshaw Index (HBI):**

<table>
<thead>
<tr>
<th>Date:</th>
<th>Current weight:</th>
<th>Time period of weight loss:</th>
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</table>

Please specify which drugs patient has previously received

<table>
<thead>
<tr>
<th>Start date</th>
<th>Stop date</th>
<th>Treatment &amp; Dose</th>
<th>Reason for stopping</th>
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<tbody>
<tr>
<td></td>
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### CHOICE OF ANTI-TNF
NICE states that treatment should normally be started with the less expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration. In adults with severe active Crohn’s disease, **Adalimumab is NORMALLY the less expensive drug.**

NICE TA 187 recommends Infliximab 5mg/kg for adults with fistulating Crohn’s disease

If infliximab is the anti-TNF of choice in adults with severe active Crohn’s disease please indicate the clinical rationale for this choice over adalimumab.

<table>
<thead>
<tr>
<th>ADALIMUMAB:</th>
<th>INFliximAB:</th>
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<tbody>
<tr>
<td>Dose at Week 0:</td>
<td>Weight(kg)</td>
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<tr>
<td>Week 2:</td>
<td>Frequency of administration:</td>
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<tr>
<td>Week 4 onwards:</td>
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### Treatment failure before 12 months (see appendix 1)
Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter.

When stopped between 12 weeks and 1 year please give reason for discontinuation:

Date of discontinuation:...........................................

For continued maintenance treatment patients should show clear response to induction therapy as outlined in Appendix 1. Benefit should be clear cut at 6 months. Otherwise they are deemed to have failed anti-TNF treatment

Is the patient suitable for continuation of treatment by demonstrating a reduction of HBI of > 2 after induction: ☐ Yes / ☐ No

HBI at 6 months:...... Continue treatment?: ☐ Yes / ☐ No

### Reviewing treatment after 12 months (see appendix 2)
All patients starting anti-TNF therapy should be informed that there will be an attempt to withdraw treatment in line with NICE TAG 187 12 months after treatment.

Confirm that stopping treatment has been discussed with patient::
### Dose escalation or interval reduction to recapture remission (see Appendix 3)

Commissioners will not ROUTINELY fund dose escalation for maintenance.

**Dose escalation for infliximab is for** up to 3 doses. Interval may be shortened to 6 or 4 weeks at 5mg/kg; or 3x 10mg/kg infusions.

Dose escalation for adalimumab: 40mg weekly for 8 doses

Following dose escalation, the dosage will revert to the usual maintenance level with patients’ needs reassessed. High dose maintenance requires separate, patient-specific approval stating rationale.

<table>
<thead>
<tr>
<th>Proposed drug:</th>
<th>Dose:</th>
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<table>
<thead>
<tr>
<th>Frequency:</th>
<th>Length of dose escalation for:</th>
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<tr>
<th>Rationale for dose escalation:</th>
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I acknowledge and adhere to the cost effective usage of biologicals as advocated in NICE TA187, and believe that within this Trust the above patient would be best managed using the biological requested above.

**Consultant name:**…………………………………

**Date:**……………………………

**Signature:**………………………………………………

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Has this application been reviewed by another consultant experienced in the therapeutic management of Crohn’s Disease.  ☐ Yes / ☐ No

If yes, state name below:

**Name:**……………………………………………………

**Date:**……………

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I confirm that the patient (or in the case of a minor or vulnerable adult where the parent/guardian or legal carer) has given consent for the patient identifiable data on this form to be shared with the CCG Medicines Management / Optimisation or Contracts Team. This data may then be used 1. In the interests of the care of the patient. 2. For clinical audit purposes. 3. To validate against subsequent invoices.

| _ Yes |
| _ No |

**Signature (or email confirmation) by Trust Chief Pharmacist (or deputy)**

**Name:**

**Date:**

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**For CCG Use**

**CCG Informed:** Date……………………………by:……………………………

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### Monitoring Sheet

**For:**

<table>
<thead>
<tr>
<th>Patient Initials</th>
<th>D.O.B</th>
<th>NHS Number</th>
</tr>
</thead>
</table>

**Following initiation of treatment:**

*Funding will only be approved after 12 weeks and 6 months if evidence of therapeutic benefit. Treatment will usually be stopped after 12 months – see appendix 2. Where treatment is stopped, the CCG must be informed by 15th of the month following that in which treatment cessation occurred.*

<table>
<thead>
<tr>
<th>Date</th>
<th>Time on treatment</th>
<th>Drug / dose / freq</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>2 weeks</td>
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<tr>
<td></td>
<td>8 weeks</td>
<td>12 weeks</td>
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<tr>
<td></td>
<td>6 months</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>24 months</td>
<td>36 months</td>
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<tr>
<td></td>
<td>48 months</td>
<td>60 months</td>
</tr>
</tbody>
</table>

**HBI**

- Well being (0-4)
- Abdo pain (0-3)
- No. Liquid Stools
- Abdo Mass (0-3)
- Complications
- **TOTAL**

**CRP / ESR**

- ../..
- ../..
- ../..
- ../..
- ../..
- ../..
- ../..
- ../..
- ../..
- ../..
- ../..

**Calprotectin**

**Colonoscopy**

**Treatment**

**Recommendation**

**Harvey Bradshaw Index (HBI):**

- General well-being (0 = well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible)
- Abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe)
- Number of liquid stools per day
- Abdo mass (0 = none, 1 = dubious, 2 = definite, 3 = definite and tender)
- Complications: arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, new fistula, abscess (score 1 per item)

CRP should also be monitored (and faecal calprotectin where available) to corroborate HBI – all should be done 8 weekly

HBI score can be disproportionately influenced by the ‘number of liquid stools per day’. Some discretion may be required particularly in patients who have loose stools when in remission.
Appendix 1 - Guidance on withdrawal of anti-TNF therapy in Crohn’s disease due to failure to respond or insufficient response to warrant continued treatment

**Infliximab**
- Patients are scheduled to receive infliximab induction course of 0, 2 and 6 week infusions of 5mg/kg and then 2 monthly thereafter
- Assess 6 weeks after 1st dose (i.e. having had ‘week 0’ and ‘week 2’ infusions but before getting ‘week 6’)
  - If no symptomatic response (improvement in clinical symptoms, or fall of HBI ≤2 points, or no reduction in fistulae drainage)
    - => no further infliximab; consider surgery
  - If remission achieved (total HBI score ≤4 – correlates with CDAI<150; or >50% improvement in fistula drainage)
    - => continue with week 6 and 8 weekly infusions thereafter
  - If partial response (fall of HBI >3 points – correlates with fall of CDAI of >100 - but no remission) then give ‘week 6’ dose and re-evaluate at week 12
    - => If remission achieved (total HBI score ≤4) => continue with 8 weekly infusions
    - => If HBI ≥5 consider surgery if appropriate

**Adalimumab**
- Patients are scheduled to receive adalimumab induction course of 160mg then 80mg at 2 weeks then 40mg every other week. An alternative induction regime is 80mg at week 0 and thereafter 40mg every other week – but this is associated with greater need for high dose maintenance therapy.
- First assessment between week 8-10
  - If no symptomatic response to first 4 doses (improvement in clinical symptoms, or fall of HBI ≤2 points, or no reduction in fistulae drainage)
    - => no further adalimumab; consider surgery if appropriate
  - If remission achieved (total HBI score ≤4 – correlates with CDAI<150; or >50% improvement in fistula drainage)
    - => continue with 40mg adalimumab every other week
  - If partial response (fall of HBI >3 points – correlates with fall of CDAI of >100 - but no remission)
    - => then give week 10 dose and re-evaluate at week 12.
  - If remission achieved (total HBI score ≤4)
    - => continue with 2 weekly injections
  - => If HBI ≥5 consider surgery if appropriate
Appendix 2. Criteria for stopping biologicals at 1 year with monitoring plan.

- All patients starting anti-TNF therapy should be informed that there will be an attempt to wean this at 1 year

- From 8 months patients should be established on an optimised dose of immunomodulator therapy (azathioprine 2.5 mg/kg/day; 6MP 1.5 mg/kg/day; methotrexate 15-25mg total dose once per week)

- Situations in which the ‘1 year wean’ should be attempted include:
  - Patients not previously treated with optimised dose of immunomodulator therapy prior to starting infliximab (e.g. may happen in the context of acute severe steroid-refractory Crohn’s disease)
  - Patients with surgically amenable Crohn’s disease: most commonly this will be limited ileo-caecal disease - i.e. where limited surgical resection (ideally laparoscopic) would remove diseased segment without expectation of stoma or short bowel syndrome
  - Patients in deep remission (normal CRP, normal colonoscopy +/- normal calprotectin) but who have had particularly troublesome Crohn’s prior to starting anti-TNF therapy (e.g. pan-enteric, multiple small bowel resections / risk of short bowel syndrome, complex peri-anal or rectal disease with significant risk of permanent ileostomy etc) – consider stretching interval between doses as prelude to stopping (e.g. stretch interval to 10, 12 then 14 weeks – if no relapse at 14 weeks then stop)
  - For patients who have been on anti-TNF therapy long-term, with no previous discussion about stopping, may find the concept of interval stretch with a view to stopping easier than just stopping

- All patients in whom anti-TNF therapy is stopped should be monitored closely for evidence of relapse. Only by careful documentation, including continuing HBI, and CRP 3-6 monthly +/- colonoscopy / faecal calprotectin + number of hospitalizations / surgeries / days off work will we understand the impact of implementing a ‘stopping strategy’. I suggest we aim to pool data and write up after 2/3/5 years.

TA 187 sets out that people whose disease relapses after treatment is stopped should have the option to start treatment again. At that point an updated GPA must be completed and returned to the CCG of the practice where the patient is then registered

Appendix 3. Dose Escalation / Interval Shortening

- For patients who have responded to a conventional induction and treatment regime but then lost response it is worth attempting to recapture with a temporary period of increased dose / shortened interval between doses. The literature favours the latter but practise varies. One such regime would be up to 3 doses of Infliximab 5mg/kg given 4-6 weekly and then stretch back to 8 weekly; or up to 8 weeks on weekly adalimumab 40mg then stretch back to every other week.

- A significant proportion of patients who respond to the shortened interval will remain in remission as the interval is stretched back to 8 weekly (infliximab) or 2 weekly (adalimumab)

- A temporary period of ‘interval shortening’ to recapture response does not require prior approval from any formal committee, but the intention to do this should be flagged by submitting an updated GPA form. A note can then be made so your Trust is not challenged for the amount charged.

- NB Prior approval is required for long-term dose escalation - defined as beyond 3 doses for infliximab, or beyond 8 doses for adalimumab.

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