Adult with active Crohn’s disease

Does the adult have severe active Crohn’s disease?

**Severe active Crohn’s disease** is defined as very poor general health and one or more symptoms such as:
- Weight loss
- Fever
- Severe abdominal pain
- Usually frequent diarrhoeal stools (≥ 3 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:
- Crohn’s disease activity index score (CDAI) > 300
- Harvey-Bradshaw score of ≥ 8-9

Has the patient’s disease failed to respond to or is the patient intolerant of or does the patient have contraindications to conventional therapy, including:
- Immunosuppressive treatments and/or
- Corticosteroid treatments?

Does the adult have active fistulising Crohn’s disease?

Has the patient’s disease failed to respond to or is the patient intolerant of or does the patient have contraindications to conventional therapy, including:
- Antibiotics and
- Drainage and
- Immunosuppressive treatments?

Optimise pre-biologic treatment

Go to Pathway A
Adult with severe active Crohn’s disease

Go to Pathway B
Adult with active fistulising Crohn’s disease

Commissioners and clinicians should refer to the relevant technology appraisal for each biologic drug for further information about their eligibility and prescription.
SWL Drug Pathway – Crohn’s Disease
Version 3 (Oct 2018) (based on NICE Crohn’s disease commissioning algorithm - with local adaptation)

Pathway A: Severe active Crohn’s Disease

**Note 1:** Choose ONE drug per step (note that step 2 is optional) before moving onto the next step due to primary or secondary treatment failure.
If there is more than one NICE approved treatment available, NICE recommends a discussion between the responsible clinician and the patient about the advantages and disadvantages of each treatment (considering therapeutic need and likely adherence to treatment). If more than one treatment option is suitable, the least expensive will be chosen (taking into account administration costs, dosage and price per dose) unless an order of preference is stated in the TAs. The SWL drug choices in this algorithm are based on cost (using list price or nationally (NICE) / locally (LPP) agreed contract prices).

**Note 2:** Consider alternative drug from the same step in the treatment pathway if patient has responded to CCG approved drug treatment but this had to be stopped due to an adverse event after initiation.

**Note 3:** Contraindications, cautions and information on malignancies [see overleaf]

**Note 4:** Treatment response
At 12 weeks (adalimumab), 6 weeks (Infliximab), 14 weeks (vedolizumab), 16 weeks (ustekinumab) after the start of treatment, people should have their disease reassessed to determine whether patients are responding adequately and if ongoing treatment is still appropriate. Treatment should only be continued if there is clear evidence of response to drug treatment defined by a decrease in Harvey-Bradshaw Index by ≥3 points or CDAI by ≥70 points.

**Note 5:** Dose escalation is allowed temporarily as per NICE or local agreement for:
- Adalimumab weekly for up to 12 weeks
- Infliximab 10mg/kg for 3 doses
- Infliximab 5mg/kg six to four weekly for up to 12 weeks
- Ustekinumab 90 mg 8 weekly for 16 weeks with extension to 1 year
On-going dose escalation for maintenance is not routinely commissioned and will require submission of an IFR demonstrating that patient specific exceptional clinical circumstances exist.

Dose escalation is not routinely commissioned for:
- Vedolizumab

**Step 1:** Use least expensive drug as a planned course of treatment (note 1&2)
- Adalimumab (TA187) or
- Infliximab biosimilar (TA187)

Local agreement: Ustekinumab reserved for use after TNF-alpha inhibitors

**Step 2:** Local agreement
Use alternative TNF-alpha inhibitor if considered appropriate (note 1&2)
- Adalimumab or
- Infliximab biosimilar

**Step 3:**
1st choice: Ustekinumab (TA456) or
2nd choice: Vedolizumab (TA352) (if unable to use SC alternative)

At any point before 12 months of treatment has passed, has treatment failed (including the need for surgery)? (note 4&5)

**Note 6:** Disease reassessment
At 12 months after the start of treatment, people should have their disease reassessed to determine whether ongoing treatment is still clinically appropriate. Treatment should only be continued if there is clear evidence of ongoing active disease. This should be determined by:
- Clinical symptoms and
- Biological markers and
- Investigation, including endoscopy if necessary

**Note 7:** Funding requests for treatment outside this commissioned pathway can be made via the Individual Funding Request (IFR) process to the relevant commissioning organisation (see www.swlmcg.nhs.uk for IFR policy and application form)

**1st choice:** Ustekinumab (TA456) or
2nd choice: Vedolizumab (TA352) (if unable to use SC alternative)

At any point before 12 months of treatment has passed, has treatment failed (including the need for surgery)? (note 4&5)

**Optional Step 2:**
Local agreement
Use alternative TNF-alpha inhibitor if considered appropriate (note 1&2)
- Adalimumab or
- Infliximab biosimilar

At any point before 12 months of treatment has passed, has treatment failed (including the need for surgery)? (note 4&5)

**Step 4:** Local agreement
- Vedolizumab

At any point before 12 months of treatment has passed, has treatment failed (including the need for surgery)? (note 4&5)

**Discontinue drug treatment (note7)**

**Note 7:** Funding requests for treatment outside this commissioned pathway can be made via the Individual Funding Request (IFR) process to the relevant commissioning organisation (see www.swlmcg.nhs.uk for IFR policy and application form)
Step 1: Use Infliximab biosimilar as a planned course of treatment (TA187)

At any point before 12 months of treatment has passed, has treatment failed (including the need for surgery)? (note 4&5)

Yes  No

Discontinue biologic treatment (note 7)

At 12 months after the start of treatment, reassess the disease (note 6). Is there evidence of on-going active disease?

Yes  No

Is the patient in stable clinical remission?

Yes

Discuss the risks and benefits of continued treatment. Is a trial withdrawal considered appropriate?

No

Maintain treatment and reassess patient at least every 12 months

Trial withdrawal from biologic drug used. Restart treatment if patient relapses after treatment is stopped

Note 4: Treatment response
At 6 weeks (infliximab) after the start of treatment, people should have their disease reassessed to determine whether patients are responding adequately to treatment and if ongoing treatment is still appropriate. Treatment should only be continued if there is clear evidence of response to biologic treatment defined by a decrease in Harvey-Bradshaw Index by ≥ 3 points or CDAI by ≥ 70 points.

Note 5:
Dose escalation is allowed temporarily as per local agreement:
• Infliximab 10mg/kg for 3 doses
• Infliximab 5mg/kg six to four weekly for up to 12 weeks
Ongoing dose escalation for maintenance is not routinely commissioned and will require submission of an IFR demonstrating that patient specific exceptional clinical circumstances exist.

Note 6: Disease reassessment
At 12 months after the start of treatment, people should have their disease reassessed to determine whether ongoing treatment is still clinically appropriate. Treatment should only be continued if there is clear evidence of ongoing active disease. This should be determined by:
• Clinical symptoms and
• Biological markers and
• Investigation, including endoscopy if necessary

Note 7:
Funding requests for treatment outside this commissioned pathway can be made via the Individual Funding Request (IFR) process to the relevant commissioning organisation (see www.swlmcg.nhs.uk for IFR policy and application form)
Note 3: Contraindications, cautions and information about malignancies

NOTE: The information in Table 1 and 2 is not exhaustive. Please also consult the current Summary of Product Characteristics (SPC) for the respective drugs prior to prescribing for up to date prescribing information, including detailed information on adverse effects, drug interactions, cautions and contraindications (available via www.medicines.org.uk).

Table 1: Contraindications

<table>
<thead>
<tr>
<th>TNF-alpha inhibitors</th>
<th>Ustekinumab</th>
<th>Vedolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypersensitivity to active substance or excipients</td>
<td>• Hypersensitivity to active substance or excipients</td>
<td>• Hypersensitivity to active substance or excipients</td>
</tr>
<tr>
<td>• Active TB and other severe infections (sepsis, abscesses) and opportunistic infections</td>
<td>• Clinically important, active infection (eg active TB)</td>
<td>• Active severe infections such as TB, sepsis, CMV, listeriosis, and opportunistic infections such as PML</td>
</tr>
<tr>
<td>• Moderate to severe heart failure (NYHA class III/IV)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Cautions

<table>
<thead>
<tr>
<th>TNF-alpha inhibitors</th>
<th>Ustekinumab</th>
<th>Vedolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Infections (impaired lung function)</td>
<td>• Chronic infections or history of recurrent infections</td>
<td>• No identified systemic immunosuppressive activity but effects on systemic immune system function in patients with IBD not known</td>
</tr>
<tr>
<td>• Hepatitis B reactivation</td>
<td>• Malignancies – no studies</td>
<td>• The risk of malignancy is increased in patients with ulcerative colitis and Crohn's disease. Immuno-modulatory medicinal products may increase the risk of malignancy</td>
</tr>
<tr>
<td>• Demyelinating diseases</td>
<td>• Non-melanoma skin cancer (&gt; 60 years of age, history of prolonged immunosuppressant therapy, PUVA)</td>
<td>• Malignancies not listed as side effect</td>
</tr>
<tr>
<td>• Malignancies – lymphomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Non-melanoma skin cancer (history of prolonged immunosuppressant therapy, PUVA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mild heart failure (NYHA class I/II)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Autoimmune processes (Lupus)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Immunosuppressant therapies to use or avoid in IBD patients with a history of cancer [adapted from Beaugerie L, 2014] - Ref: European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies. ECCO. *Journal of Crohn’s and Colitis*, 2015, 945-965

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Avoid</th>
<th>Use with caution</th>
<th>Can be used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>Thiopurines</td>
<td>Anti-TNF, methotrexate, steroids</td>
<td>Methotrexate, steroids</td>
</tr>
<tr>
<td>Acute myeloid leukaemia and severe myelodysplastic disorders</td>
<td>Thiopurines</td>
<td>Anti-TNF</td>
<td>Methotrexate, steroids</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Anti-TNF</td>
<td>Thiopurines, steroids</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>Thiopurines</td>
<td>Anti-TNF, steroids</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Urinary tract cancer</td>
<td>Thiopurines</td>
<td>Anti-TNF</td>
<td>Methotrexate, steroids</td>
</tr>
<tr>
<td>Other tumours</td>
<td>Thiopurines, anti-TNF</td>
<td>Methotrexate, steroids</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Risk of cancer occurrence [adapted from Penn I, 1993]  
Ref: European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies (ECCO. *Journal of Crohn’s and Colitis*, 2015, 945-965)

<table>
<thead>
<tr>
<th>Risk</th>
<th>Organ/type of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low [&lt; 10%]</td>
<td>Incidental asymptomatic renal tumour</td>
</tr>
<tr>
<td></td>
<td>Lymphomas</td>
</tr>
<tr>
<td></td>
<td>Testicle</td>
</tr>
<tr>
<td>Intermediate [11-25%]</td>
<td>Uterine body</td>
</tr>
<tr>
<td></td>
<td>Colon</td>
</tr>
<tr>
<td>High [&gt;25%]</td>
<td>Bladder</td>
</tr>
<tr>
<td></td>
<td>Sarcoma</td>
</tr>
</tbody>
</table>
### SWL Drug Pathway – Crohn’s Disease

**Version 3 (Oct 2018)** *(based on NICE Crohn’s disease commissioning algorithm - with local adaptations)*

<table>
<thead>
<tr>
<th>Version number</th>
<th>Amendments made</th>
<th>Date of approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>26 May 2011</td>
</tr>
</tbody>
</table>
| 1.0            | Include approved recommendations from South West London Biologics Care Pathway Review for Inflammatory Bowel Disease (IBD) (8 Feb 2017):  
• Local agreement – allow use of alternative TNF-alpha inhibitor (adalimumab or infliximab) if appropriate (step 2)                                                                                                                                                                       | 27 Feb 2017      |
| 2.0            | Include approved recommendations from SWL IBD network meeting (28 Jun 2017):  
• Preferred drug choices  
• Ustekinumab (NICE TA 456) in step 1 (only if anti-TNF contraindicated/not tolerated (local agreement)) and in step 3  
• New local agreement: vedolizumab step 4  
• Add existing agreements on dose escalation  
• Add dose escalation with ustekinumab in line with license and NICE TA  
• Add contraindications and information on cancer risk  
• Improved pathway presentation                                                                                                                                                                                                                                                      | 01 Nov 2017      |
| 2.1            | Amend note 1 to clarify that a discussion between the responsible clinician and the patient should take place about the advantages and disadvantages of each treatment (considering therapeutic need and likely adherence to treatment) and if more than one treatment option is suitable, the least expensive will be chosen (taking into account administration costs, dosage and price per dose) unless an order of preference is stated in the TAs.                                                                 | 11 Jan 2018      |
| 3.0            | Include approved recommendations from SWL IBD network meeting (12 Jul 2018):  
• Change presentation to clarify that step 2 is an optional step and not mandated (local agreement)  
• Change pathway presentation to clarify that TNF-alpha inhibitors are not currently commissioned after ustekinumab or vedolizumab  
• Include note 7 - reference to IFR process                                                                                                                                                                                                                                         | 08 Oct 2018      |

**Date of next review:** October 2020 *(or earlier if indicated)*