High Cost Drugs Pathways for Inflammatory Bowel Disease in Adults (including biologics)

June 2019

Version 3.0
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DOCUMENT CONTROL

Revision history

The latest and master version of this document is held on the GMMMG website.

REVISION DATE	ACTIONED BY	SUMMARY OF CHANGES	VERSION
September 2017	IBD working group	Added ustekinumab following publication of NICE TA456	1.1
October 2017	IBD working group	Changes to special situations	1.2
November 2017	IBD working group	Changes made following consultation	1.3
November 2017	Sarah Jacobs	Final changes to vaccinations & special situations. Amendments to flow charts.	1.4
March 2019	Anna Pracz	Added tofacitinib as per NICE TA547. Minor amendments to reflect addition of non-biologic high cost drug to the guideline. Changes to the special considerations & vaccinations section.	2.1
April 2019	Anna Pracz	Amended as per steering group's comments	2.2
May 2019	Anna Pracz	Amended as per final comments on draft 1.6 from the steering group. Incorporation of NICE NG129, NICE NG130 and MHRA's tofacitinib safety alert with changes to the document as relevant. Optimal infliximab trough levels on pathway C amended following results of PANTS study.	2.3
June 2019	Anna Pracz	Final draft presented to HCDOG and approved.	3.0

Approvals

This document must be approved by the following before distribution:

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IBD working group	March 2019	2.3
HCDOG	June 2019	3.0
GMMMG	June 2019	3.0

Final version available on GMMMG website http://gmmmg.nhs.uk/

Contents

High Cost Drugs Pathways for Inflammatory Bowel Disease in Adults

1. Background

These pathways are to be used as guidelines in the initiation and maintenance of high cost drugs in the management of inflammatory bowel disease (IBD). These pathways have been written using up to date published research and evidenced based medicine. This has been a clinical project implemented by MAHSC and a joint project between the gastroenterology departments of the Greater Manchester hospital trusts.

Currently the pathways include biologic agents: tumour necrosis factor inhibitors (anti-TNFs; infliximab, adalimumab and golimumab), an integrin inhibitor (vedolizumab), and an interleukin inhibitor (ustekinumab). More recently, a novel therapy with a non-biologic high cost drug, a Janus kinase inhibitor (JAK-inhibitor; tofacitinib), has been made available as a treatment option for patients with ulcerative colitis.

2. NICE guidance

The links to relevant NICE guidance are listed below. Any new high cost drugs that are approved by NICE between GMMMG IBD pathway iterations will be considered for placement in this pathway. The use of any new NICE approved high cost drugs prior to inclusion in the pathway will be allowed, provided that the total number of drugs allowed in pathway has not been exceeded. Those drugs should be used in accordance with the relevant NICE TA.

The NICE recommendations also apply to biosimilar drugs, where marketing authorisations allow use of the biosimilar for the indication specified in the relevant NICE TA.

2.1. Crohn's disease

NICE (2019): Crohn's disease: management NG129

2.1.1. NICE (2010): Infliximab and adalimumab for the treatment of Crohn's disease TA187

Infliximab and adalimumab, are recommended as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (immunosuppressive and/or corticosteroid) or who are intolerant of or have contraindications to such therapy.

Severe active Crohn's disease is defined as very poor general health, plus ≥1 symptom of: weight loss, fever, severe abdominal pain, and 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 > 300, or a Harvey-Bradshaw score of >8 (see section 11).

Infliximab is recommended as treatment option for people with active fistulising Crohn's disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy.

Infliximab or adalimumab should be given until treatment failure, or the need for surgery, or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed to determine whether on-going treatment is still clinically appropriate. Treatment should only

be continued if there is clear evidence of on-going active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary.

People who continue treatment should have their disease reassessed at least every 12 months to determine whether on-going treatment is still clinically appropriate.

A trial withdrawal should be considered in patients in stable clinical remission.

People whose disease relapses after treatment is stopped should have the option to start treatment again.

2.1.2. NICE (2015): Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy TA352

Vedolizumab is recommended as an option for treating moderately to severely active Crohn's disease only if a tumour necrosis factor-alpha inhibitor has failed (that is, the disease has responded inadequately or has lost response to treatment), or a tumour necrosis factor-alpha inhibitor cannot be tolerated or is contraindicated.

Vedolizumab should be given as a planned course of treatment until it stops working or surgery is needed, or until 12 months after the start of treatment, whichever is shorter.

At 12 months, people should be reassessed to determine whether treatment should continue. Treatment should only continue if there is clear evidence of on-going clinical benefit. People who continue vedolizumab should be reassessed at least every 12 months to decide whether continued treatment is justified. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse.

Vedolizumab is recommended only if the company provides it with the discount agreed in the patient access scheme.

2.1.3. NICE (2017): Ustekinumab to treat moderately to severe Crohn's disease after previous treatment TA456

Ustekinumab is recommended, within its marketing authorisation, as an option for treating moderately to severely active Crohn's disease, that is, for adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or anti-TNF or have medical contraindications to such therapies.

The choice of treatment between ustekinumab or another biological therapy should be made on an individual basis after discussion between the patient and their clinician about the advantages and disadvantages of the treatments available.

Ustekinumab should be given until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed in accordance with NICE's recommendations for infliximab and adalimumab for the treatment of Crohn's disease (NICE TA187) to see whether treatment should continue.

2.2. Ulcerative colitis

NICE (2019): Ulcerative colitis: management NG130

2.2.1. NICE (2015): Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy TA329

Infliximab, adalimumab and golimumab are recommended, as options for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy (e.g. corticosteroids, mercaptopurine or azathioprine), or who cannot tolerate them, or who have a medical contraindication for such therapies.

The choice of treatment between infliximab, adalimumab or golimumab should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available. This should take into consideration therapeutic need and whether or not the patient is likely to adhere to treatment and the cost of intervention.

Golimumab is recommended only if the company provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, as agreed in the patient access scheme.

Therapy should be given as a planned course until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. The treatment should be continued only if there is clear evidence of response as determined by clinical symptoms, biological markers and investigation including endoscopy if necessary.

People who continue treatment should be reassessed at least every 12 months to determine whether on-going treatment is still clinically appropriate.

A trial withdrawal from treatment should be considered for all patients who are in stable clinical remission. People whose disease relapses after treatment is stopped should have the option to start treatment again.

2.2.2. NICE (2008): Infliximab for acute exacerbations of ulcerative colitis TA163

Infliximab is recommended as an option for the treatment of acute exacerbations of severely active ulcerative colitis. It is only recommended in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient. Infliximab in this guidance relates to only an induction course of three doses of infliximab.

Treatment of acute exacerbations of UC with infliximab or ciclosporin should be the decision of the responsible gastroenterologist.

The guidance on continuation of treatment is covered by NICE TA329 (see section 2.2a).

2.2.3. NICE (2015): Vedolizumab for treating moderately to severely active ulcerative colitis TA342

Vedolizumab is recommended as an option for treating moderately to severely active ulcerative colitis only if the company provides vedolizumab with the discount agreed in the patient access scheme.

Vedolizumab should be given until it stops working or surgery is needed.

At 12 months after the start of treatment, people should be reassessed to see whether treatment should continue. Treatment should only continue if there is clear evidence of on-going clinical benefit. People

who continue vedolizumab should be reassessed at least every 12 months to see whether continued treatment is justified. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse.

2.2.4. **NICE (2018): Tofacitinib for moderately to servery active ulcerative colitis TA547**

Tofacitinib is recommended as an option for treating moderately to severely active ulcerative colitis in adults when conventional therapy or a biological agent cannot be tolerated or the disease has responded inadequately or lost response to treatment. Tofacitinib is only recommended if it is provided with the discount agreed in the patient access scheme.

The initial induction therapy should be assessed after 8 weeks and subsequent maintenance continued in line with the summary of product characteristics (patients whose disease has not responded adequately to tumour necrosis factor antagonist therapy, a higher maintenance dose may be considered) .

The induction therapy can be extended to a total of 16 weeks and should be stopped if there is no evidence of therapeutic benefit by week 16.

3. Initiating treatment with a biological medicine

The choice of biologic used should be guided by clinical judgement, national or local guidance, and the overall value proposition offered by the individual medicines. The rationale for choice should be documented.

If more than one treatment is suitable, the least expensive product should be chosen (taking into account administration costs, dosage, price per dose and treatment frequency).Where biosimilars are available the best value product should be used. See GMMMG (2016): Prescribing of high cost biosimilar biological medicines.

If the least expensive product is not prescribed, the reasons why must be documented and made available to commissioners if required.

In line with the MHRA guidance (2008): Biosimilar products, biologics including biosimilars must be prescribed by brand name (i.e. the brand of biosimilar or originator product) to support on-going pharmacovigilance of the individual products.

Pharmacovigilance is essential for any new biological medicine including biosimilars and additional monitoring is indicated through the MHRA's Black Triangle Scheme. Patients prescribed a biologic should be enrolled on to the relevant biologic registry which serves data collection on the safety and effectiveness of medicines in clinical practice.

4. Biosimilars

Use of biosimilars has become routine clinical practice. All NICE guidance on biologics applies to biosimilar medicines.

In February 2016 the British Society of Gastroenterology published guidance on the use of biosimilar infliximab in inflammatory bowel disease:

BSG (2016): Guidance on the Use of Biosimilar Infliximab in Inflammatory Bowel Disease

The guidance states that there is sufficient data from observational studies to show that safety and clinical efficacy of biosimilar infliximab are comparable to the originator drug, with similar immunogenicity, and that switching from Remicade to a biosimilar is safe and effective.

4.1. Switching from originator to a biosimilar

There is accumulating evidence that patients who are in a stable clinical response or remission may be changed over to a biosimilar at the same dose and dose interval as the originator drug. This should only be done after discussion and agreement with individual patients with an explanation for the reason for changing.

The switch from a biologic originator medicine to a biosimilar should be done at the point of prescribing and not at the point of dispensing or administration.

5. Individual funding requests (IFR)

- IFRs for Crohn's disease will not be required for any of the 4 high cost drugs included in this pathway.

- IFRs for ulcerative colitis will not be required for any of the 4 high cost drugs included in this pathway.

- All treatment options exceeding the allowed number of high cost drugs or treatment with drugs not included in this pathway (unless these have been approved by NICE and not yet included in the pathway) will require commissioner's funding approval via IFR prior to commencing the treatment.

- Requests for urgent treatment of acute severe ulcerative colitis with high doses of infliximab (see section 9.4.) are considered a rescue intervention and do not require an IFR. A Blueteq notification form for use of infliximab in acute exacerbation can be filled in retrospectively.

6. Blueteq

Blueteq forms which comply with these pathways are available. Where Blueteq has been introduced to the trust as part of the contractual arrangements, funding approval for the tariff excluded high cost drugs will be required by submission of the relevant Blueteq form prior to treatment administration. The Blueteq forms contain a list of relevant criteria that the patient must meet in order to secure funding. Any patients who do not meet these criteria will require an IFR.

NB: A Blueteq notification form for use of infliximab in acute exacerbation of ulcerative colitis can be filled in retrospectively.

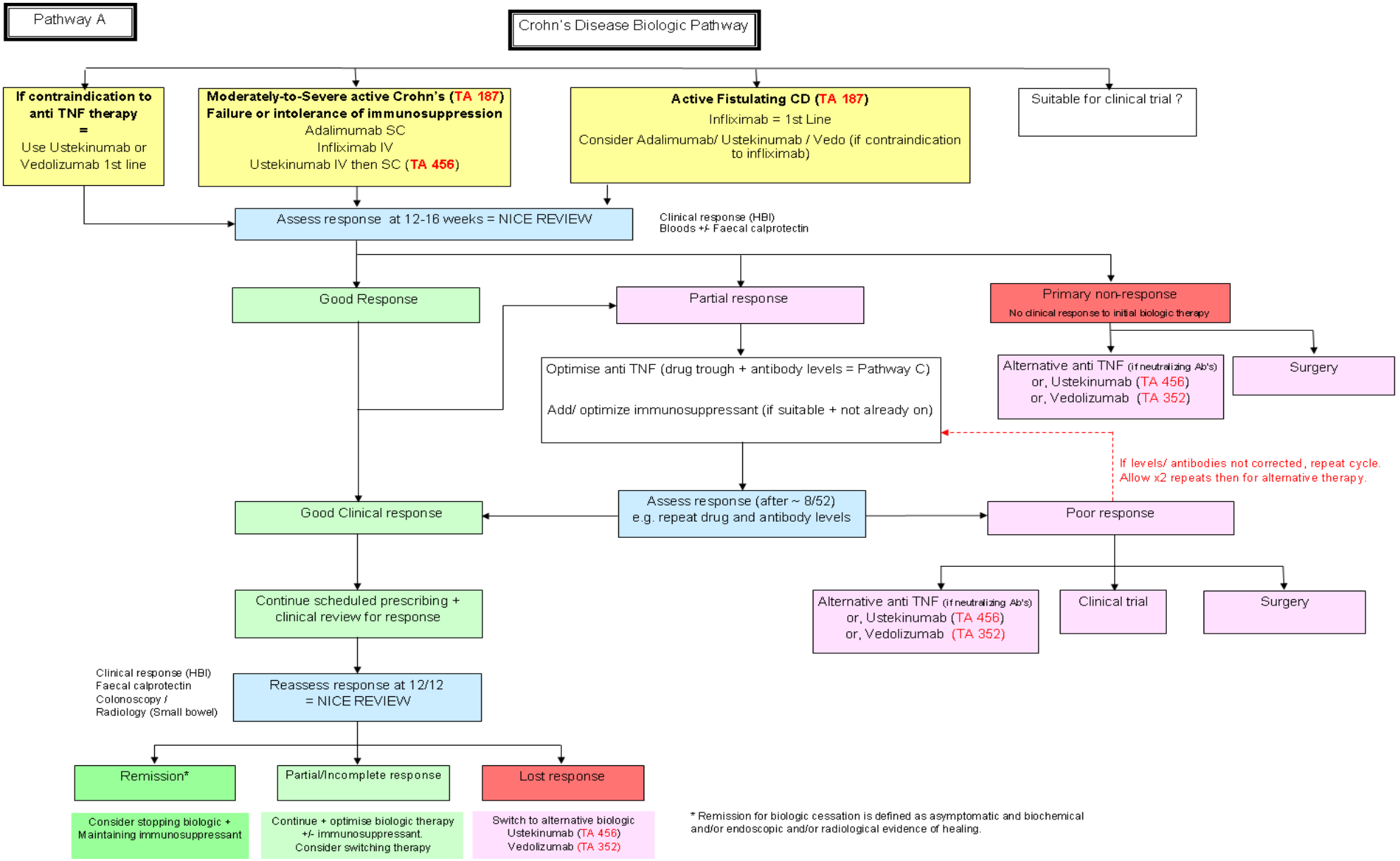
7. Checklist for patient screening on initiation of biologic agents and tofacitinib

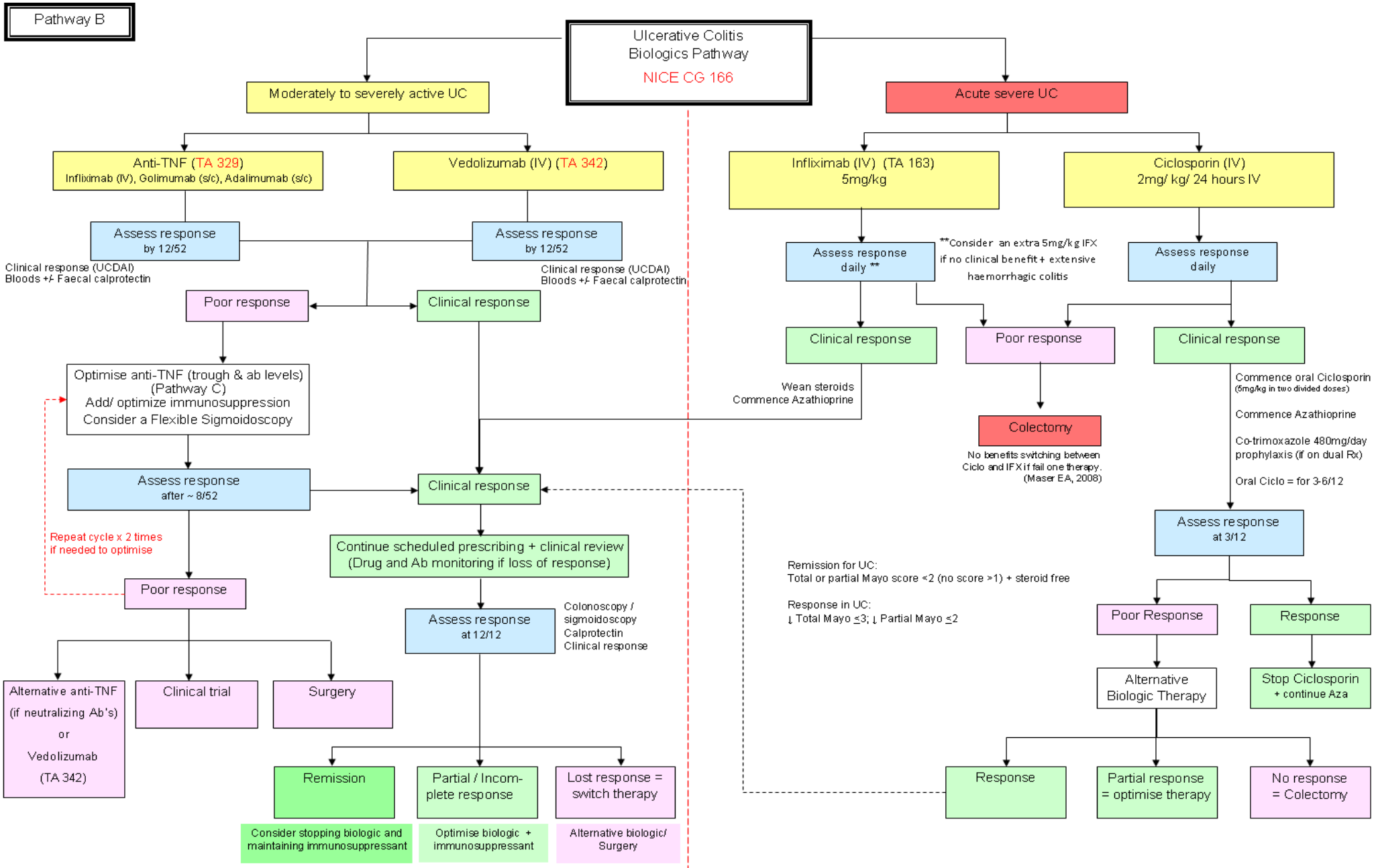
Patient's name:……**Number:**……**Consultant:**……

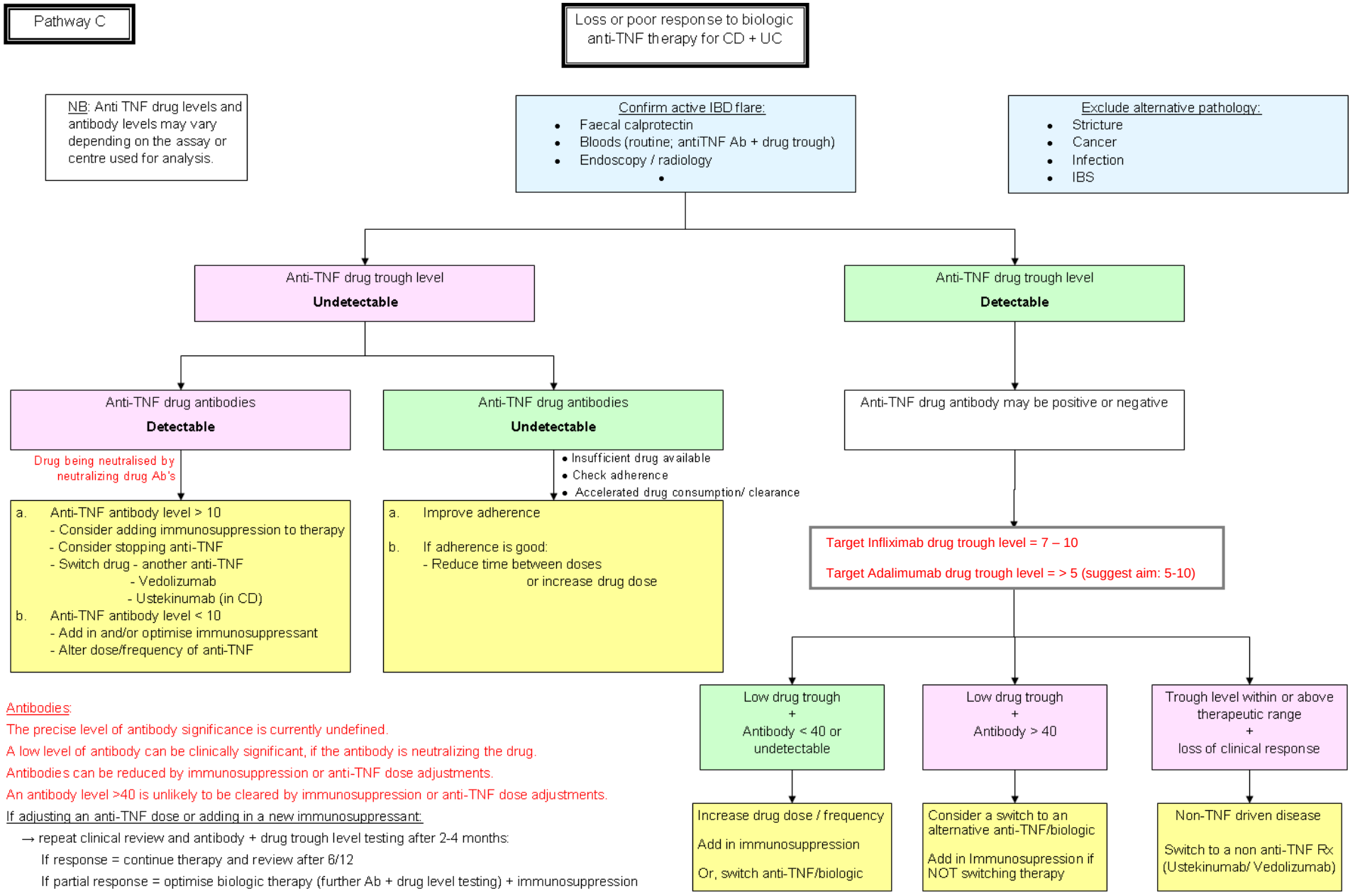
Screening Investigations Requested in Clinic	Y/N	Initial	Results/Details
FBC/U&E/LFT/CRP			
HIV **HBV** *(surface antigen, core antibody)*. *Reactivation has been reported in HbsAg-ve as well as HbsAg +ve patients stressing the importance of measuring not only HbsAg but also antibodies against HBc antigen to identify positive carrier status* **HCV** *(antibody test)* Consider **EBV, CMV** testing. *If positive result consider Hepatology/GUM referral*			
Varicella zoster IgG (If negative inform GP and patient)			
TB screening *(g-IFN testing)* *If positive refer to Respiratory Unit*			
Chest X-ray *(within the last 6 months)* **CXR checked by/date:**			
TPMT (Before commencing azathioprine therapy)			
Consider:			
Faecal calprotectin level			
Ferritin, vitamin B12, folate levels			
Screening Questions Asked in Clinic	**Y/N**	**Initial**	**Results/Details**
Previous TB/TB contact/ recent travel to high risk countries (*details*)			
History of demyelinating disorders of the CNS *(e.g. MS)* *(details)*			
History of heart failure (NYHA class III or IV) *(details)*			
Risk of pulmonary embolism (Tofacitinib contraindicated)			
History of recurrent infection *(details)*			
History of cancer *(Type/Date when occurred/Date of all clear)*			
Date of last mammogram (50yr +) *(Encourage patient to visit GP if >3 years)*			
Date of last smear (25yr +) *(Encourage patient to visit GP if >3 years)*			
History of infusion reaction to any agent *(To what/type of reaction)*			
Allergy (*details*)			
Education and Funding	**Initial**	**Details**	
Request for funding			
Pregnancy/breastfeeding advice given			
Influenza vaccine advice given			
Pneumococcal vaccine advice given			
Patient counselled and educated			
Patient education pack given			

Completing clinician's signature…… **Date**…….....

Nurse practitioner signature…… **Date**…….....


Pathway A
Crohn's Disease Biologic Pathway
If contraindication to anti TNF therapy = Use Ustekinumab or Vedolizumab 1st line
Moderately-to-Severe active Crohn's (TA 187) Failure or intolerance of immunosuppression Adalimumab SC Infliximab IV Ustekinumab IV then SC (TA 456)
Active Fistulating CD (TA 187) Infliximab = 1st Line Consider Adalimumab/ Ustekinumab / Vedo (if contraindication to infliximab)
Suitable for clinical trial ?
Assess response at 12-16 weeks = NICE REVIEW
Clinical response (HBI) Bloods +/- Faecal calprotectin
Good Response
Partial response
Primary non-response No clinical response to initial biologic therapy
Optimise anti TNF (drug trough + antibody levels = Pathway C)
Add/ optimize immunosuppressant (if suitable + not already on)
Alternative anti TNF (if neutralizing Ab's) or, Ustekinumab (TA 456) or, Vedolizumab (TA 352)
Surgery
If levels/ antibodies not corrected, repeat cycle. Allow x2 repeats then for alternative therapy.
Good Clinical response
Assess response (after ~ 8/52) e.g. repeat drug and antibody levels
Poor response
Continue scheduled prescribing + clinical review for response
Alternative anti TNF (if neutralizing Ab's) or, Ustekinumab (TA 456) or, Vedolizumab (TA 352)
Clinical trial
Surgery
Clinical response (HBI) Faecal calprotectin Colonoscopy / Radiology (Small bowel)
Reassess response at 12/12 = NICE REVIEW
Remission*
Partial/Incomplete response
Lost response
Consider stopping biologic + Maintaining immunosuppressant
Continue + optimise biologic therapy +/- immunosuppressant. Consider switching therapy
Switch to alternative biologic Ustekinumab (TA 456) Vedolizumab (TA 352)
* Remission for biologic cessation is defined as asymptomatic and biochemical and/or endoscopic and/or radiological evidence of healing.


Pathway B
Ulcerative Colitis
Biologics Pathway
NICE CG 166
Moderately to severely active UC
Acute severe UC
Anti-TNF (TA 329)
Infliximab (IV), Golimumab (s/c), Adalimumab (s/c)
Vedolizumab (IV) (TA 342)
Infliximab (IV) (TA 163)
5mg/kg
Ciclosporin (IV)
2mg/ kg/ 24 hours IV
Assess response
by 12/52
Assess response
by 12/52
Clinical response (UCDAI)
Bloods +/- Faecal calprotectin
Clinical response (UCDAI)
Bloods +/- Faecal calprotectin
Assess response
daily **
**Consider an extra 5mg/kg IFX
if no clinical benefit + extensive
haemorrhagic colitis
Assess response
daily
Poor response
Clinical response
Clinical response
Poor response
Clinical response
Optimise anti-TNF (trough & ab levels)
(Pathway C)
Add/ optimize immunosuppression
Consider a Flexible Sigmoidoscopy
Wean steroids
Commence Azathioprine
Colectomy
No benefits switching between
Ciclo and IFX if fail one therapy.
(Maser EA, 2008)
Commence oral Ciclosporin
(5mg/kg in two divided doses)
Commence Azathioprine
Co-trimoxazole 480mg/day
prophylaxis (if on dual Rx)
Oral Ciclo = for 3-6/12
Assess response
after ~ 8/52
Clinical response
Assess response
at 3/12
Repeat cycle x 2 times
if needed to optimise
Continue scheduled prescribing + clinical review
(Drug and Ab monitoring if loss of response)
Remission for UC:
Total or partial Mayo score ≤2 (no score >1) + steroid free
Response in UC:
↓ Total Mayo ≤3; ↓ Partial Mayo ≤2
Poor response
Assess response
at 12/12
Colonoscopy /
sigmoidoscopy
Calprotectin
Clinical response
Poor Response
Response
Alternative anti-TNF
(if neutralizing Ab's)
or
Vedolizumab
(TA 342)
Clinical trial
Surgery
Alternative
Biologic Therapy
Stop Ciclosporin
+ continue Aza
Remission
Partial / Incom-
plete response
Lost response =
switch therapy
Response
Partial response
= optimise therapy
No response
= Colectomy
Consider stopping biologic and
maintaining immunosuppressant
Optimise biologic +
immunosuppressant
Alternative biologic/
Surgery



Antibodies:

The precise level of antibody significance is currently undefined.

A low level of antibody can be clinically significant, if the antibody is neutralizing the drug.

Antibodies can be reduced by immunosuppression or anti-TNF dose adjustments.

An antibody level >40 is unlikely to be cleared by immunosuppression or anti-TNF dose adjustments.

If adjusting an anti-TNF dose or adding in a new immunosuppressant:

→ repeat clinical review and antibody + drug trough level testing after 2-4 months:

If response = continue therapy and review after 6/12

If partial response = optimise biologic therapy (further Ab + drug level testing) + immunosuppression

If no response = consider entry into a clinical trial / alternative biologic therapy / surgery

8. Contraindications, special warnings and precautions for treatment with drugs[1]

NB for up to date information on individual drug refer to **https://www.medicines.org.uk/emc**

8.1. Ciclosporin

Contraindications to ciclosporin

- Hypersensitivity to the active substance or to any of the excipients
- Combination with products containing *Hypericum perforatum* (St John´s Wort)
- Combination with medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP) and for which elevated plasma concentrations are associated with serious and/or life-threatening events, e.g. bosentan, dabigatran etexilate and aliskiren

Special warnings and precautions for use with ciclosporin

8.2. Anti-TNFs (infliximab, golimumab, adalimumab)

Contraindications to anti-TNFs

- Moderate or severe heart failure (NYHA class III/IV heart)
- Tuberculosis* or other severe infections such as sepsis, abscesses, and opportunistic infections
- History of hypersensitivity to the active substance, to other murine proteins, or to any of the excipients

***In acute severe ulcerative colitis waiting for result of Quantiferon test to rule out tuberculosis may not be possible. The decision should be made by the consultant gastroenterologist with referral for respiratory opinion if appropriate.

Special warnings and precautions for use with infliximab, golimumab, adalimumab

8.3. Vedolizumab

Contraindications to vedolizumab

- Hypersensitivity to vedolizumab or to any of the excipients.
- Active severe infections such as tuberculosis, sepsis, cytomegalovirus, listeriosis, and opportunistic infections such as Progressive Multifocal Leukoencephalopathy (PML)

Special warnings and precautions for use with vedolizumab

8.4. Ustekinumab

Contraindications to ustekinumab

- Hypersensitivity to the active substance or to any of the excipients
- Clinically important, active infection (e.g. active tuberculosis)

Special warnings and precautions for use with ustekinumab

8.5. Tofacitinib

Contraindications to tofacitinib

- Hypersensitivity to the active substance or to any of the excipients
- Active tuberculosis, serious infections such as sepsis, or opportunistic infections
- Severe hepatic impairment
- Pregnancy and lactation

Note: As per recent MHRA alert the 10 mg twice-daily dose of tofacitinib **must not** be prescribed in patients with one or more of the following risk factors for pulmonary embolism:

- Use of combined hormonal contraceptives or hormone replacement therapy
- Heart failure
- Previous venous thromboembolism, either deep venous thrombosis or pulmonary embolism
- Inherited coagulation disorder
- Malignancy
- Patients undergoing major surgery

Additionally, other risk factors for pulmonary embolism to be considered when prescribing tofacitinib 10 mg twice-daily are age, obesity (BMI>30 kg/m2), smoking, and immobilisation.

Special warnings and precautions for use with tofacitinib

9. Special situations

9.1. Therapeutic drug monitoring and antibody testing (where available / commissioned)

The pathways include three tumour necrosis factor-alpha inhibitors (anti-TNFs): infliximab, adalimumab and golimumab. Loss of clinical effect to anti-TNF therapy is common in gastroenterology patients.[2] Among patients treated with infliximab and adalimumab, about 30% will experience a primary non-response and up to 46% secondary loss of response. [3,4]

Currently, therapeutic drug monitoring and antibody testing (TDM) in IBD patients is available for infliximab and adalimumab and is recommended for patients exhibiting primary non-response and where a secondary loss of response to therapy is suspected as it can help to identify specific reasons for treatment failure and aid clinical decision making.[5,6] See pathway C for details.

As a biologic therapy optimisation initiative, proactive TDM (i.e. where there is no loss of response) can provide evidence for the need for continued anti-TNF therapy in individual patient and give reassurance to patients following a switch to biosimilar via demonstrable evidence of unaltered drug efficacy[7].

The blood sample for anti-TNF TDM should be collected prior to administration of the next scheduled dose of the drug to allow investigation of trough levels. The reference ranges for anti-TNF TDM may vary slightly between labs depending on the assay used.

Currently, guidance relating to antibodies and drug levels for golimumab and biologics with different mechanism of action (ustekinumab and vedolizumab) is not available.

There may be variation across GM in extent of TDM application, particularly of the proactive intervention.

9.2. Switching between treatments with different biologics

Recommendations differ on the need for a washout period when switching from one biologic to another. A theoretical risk for increased susceptibility to infection has been proposed if washout time is not adequate between biologic therapies. However, there is very little published data on this topic. The half-life of the drug (table 1), clinical circumstances of the individual patient and drug levels should be considered in each case to aid decision making.

9.3. High risk patients

9.3.1. Early onset Crohn's disease

The course of Crohn's disease may be predicted by clinical factors at diagnosis and/ or at endoscopy. Onset before 40 years of age is a risk factor for a poor disease outcome.[8] Aggressive Crohn's disease causes increased relapse rates, increased admissions to hospital, the development of penetrating disease or structuring disease or abscesses plus the need for surgery.[8]

The treating specialist could consider early introduction of immunosuppressive therapy in those with early onset and at least two of the following factors:[9]

- Extensive small bowel disease
- Deep and extensive colonic ulceration
- Perianal / rectal disease
- Stricturing disease
- More than 5kg weight loss pre-diagnosis
- The requirement of corticosteroid at diagnosis
- Steroid dependency
- Smoking (encourage smoking cessation)

9.4. Acute severe ulcerative colitis

In acute severe ulcerative colitis where infliximab rescue therapy has been necessary, an undetectable serum anti-TNF drug level corresponds with a greater colectomy risk[5]. In patients with extensive haemorrhagic colitis who have not responded to initial treatment, a higher dose of infliximab (10mg/kg loading, or a second 5mg/kg at 24-48 hours) can be considered at the discretion of the clinician in order to avoid colectomy.[5,10] This would be an immediate rescue treatment and not an individual funding request.

9.5. Surgery

9.5.1. Perioperative risk of infection

Risk of postoperative infection may be reduced by temporarily stopping treatment with a biologic or JAK-inhibitor. The safe interval remains to be determined.[2] The decision to interrupt treatment should be made following a discussion between the gastroenterology and surgical teams given the specific circumstances of each individual patient.

If a patient is to undergo an **elective surgery**, consider stopping the drug 3-5 times the half-life for the relevant drug (see table 1).

Biologic and JAK-inhibitor therapy should not delay urgent surgery.

Table 1. Half-lives of drugs included in the IBD pathway and elective surgery recommendations[1,11]

Drug name	Half-life	Last dose prior to elective surgery
Adalimumab	12-14 days	6-10 weeks
Golimumab	12-14 days	6-10 weeks
Infliximab	9 days	4-7 weeks
Ustekinumab	15-32 days	9-15 weeks
Vedolizumab	25 days	12-19 weeks
Tofacitinib	3 hours	1 week

9.5.2. Postoperative disease recurrence

Biologic therapy should be considered for the treatment of postoperative recurrence of Crohn's disease if immunosuppression with azathioprine or 6-mercaptopurine has failed or is not tolerated.[12,13,14,15]

Biologic therapy is not normally considered for prophylactic use following surgery. Biologics should not be offered to maintain remission following complete macroscopic resection of ileocolonic Crohn's disease.[15]

9.6. Pregnancy

When giving family planning advice, the clinician should consider the half-life of the drug in use, advice on length of contraception after the last dose, and existing evidence for use in pregnancy and breastfeeding and paternal exposure if the drug is to be continued. See tables 1-4 for individual drugs.

The ECCO statements on pregnancy include the following:[16]

- If conception occurs at a time of quiescent disease, the risk of relapse is the same as in non-pregnant women. Conception occurring at a time of active disease increases the risk of persistent activity during pregnancy.
- Appropriate treatment of IBD should be maintained in order to reduce the risk of disease flares during pregnancy.
- Acute flares in pregnancy carry a high risk of adverse maternal and foetal outcome, and are best treated appropriately and without delay.

The ECCO's pregnancy and IBD algorithm can be accessed here.

The data for safety of biologics and JAK-inhibitor in pregnancy and paternal exposure is limited.

The decision to continue or stop biologic agents in pregnancy needs to be individualised, taking into account alternative therapies, the severity of the mother's condition prior to therapy, the risk of a disease flare caused by cessation of therapy, and the impact of a flare on the mother and the unborn child. This should be discussed by a multi-disciplinary team.

Anti-TNFs cross the placenta and the transfer is highest in 2nd and 3rd trimesters.[1, 17] The use of infliximab and adalimumab beyond the second trimester results in neonatal levels exceeding maternal levels. This exposure can be limited by stopping treatment around gestational week 24-26 where appropriate.[14] Little is known about the use of golimumab in pregnancy. As for other anti-TNFs administration during pregnancy could affect normal immune responses in the newborn.

The use of JAK-inhibitor tofacitinib is contraindicated in pregnancy.

For patients who stop therapy during pregnancy, re-loading with biologic therapy should be considered soon after delivery.

Table 2. The compatibility of drugs with pregnancy in patients with IBD [1, 17,18]

Drug name	Compatibility with 1st trimester	Compatibility with 2nd / 3rd trimester
Adalimumab	Yes	Yes, stop by 24-26 weeks
Golimumab	Limited data available*	Limited data available*
Infliximab	Yes	Yes, stop by 24-26 weeks
Ustekinumab	Limited data available*	Limited data available*
Vedolizumab	Limited data available*	Limited data available*
Tofacitinib	Not compatible**	Not compatible**

** No adverse effect indicated in animal studies*
*** Teratogenic in animal studies*

For information on vaccination of infants exposed to anti-TNF during pregnancy see section 9.8.

9.7. Breastfeeding

A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy should be made taking into account the woman's choice on breastfeeding, the drug profile, the benefit of breastfeeding to the child, and the benefit of therapy to the woman.

There is limited data on the excretion of biologics in breast milk and level of oral absorption by infant.[14]

The manufacturers of the majority of drugs in this pathway recommend that it is not advisable to breastfeed during drug treatment or for a specified duration after treatment has stopped.[1] Since human immunoglobulins are excreted into human breast milk, a risk to the breastfeeding child cannot be excluded in case of maternal exposure to anti-TNFs. However, recently more data became available on compatibility of adalimumab with lactation, which is now deemed safe by the manufacturer.[1]

For information on vaccination of infants exposed to anti-TNF through breastfeeding see section 9.8.

Table 3. Compatibility of drugs with breastfeeding[17,18,19,20]

Drug name	Compatibility with breastfeeding
Adalimumab	Yes
Golimumab	Limited data available
Infliximab	Low risk
Ustekinumab	Limited data available
Vedolizumab	Limited data available
Tofacitinib	Avoid

9.8. Vaccination of infants exposed to drugs due to maternal treatment

MHRA advise that any infant who has been exposed to immunosuppressive treatment from the mother either in utero during pregnancy or via breastfeeding should have any **live attenuated vaccination** deferred for as long as a postnatal influence on the immune status of the infant remains possible.[21]

The MHRA have received 4 Yellow Card reports regarding neonates who have died from disseminated BCG or tuberculosis infection after exposure to an anti-TNF medicine in utero; they were probably not known to be immunosuppressed at the time of vaccination.[21]

Immunisation with live vaccines, including BCG, should be delayed for 6 months in children born of mothers who were on immunosuppressive biological therapy during pregnancy.[22]

The specialist Drugs in Lactation Information Service are confident that this risk does not exist where exposure is solely through breastfeeding. Therefore no delay in vaccination is necessary where an infant is not affected by foetal exposure. [23]

The risk of a natural rotavirus infection in infants is high. Although the vaccine is a live attenuated virus the benefit from vaccination may exceed the risk of infection. Vaccination should be discussed on an individual basis.[22]

Some studies shown detectable levels of anti-TNFs in the infant following foetal exposure which caused concerns about immune system development and negative response to vaccination.[17,18]

Current vaccination strategies with **non-live vaccines** for infants who have been exposed to a biologic medicine in utero do not differ from those for unexposed infants.[14] For the complete list of live and non-live vaccines refer to tables 4 and 6.

10. Vaccinations

10.1. Routine vaccinations

During biologic therapy, patients should receive seasonal inactivated influenza vaccine annually and pneumococcal vaccine once only. Titres may need to be measured. [1,22] For up to date information consult the Green Book. Pneumococcal vaccine should be given 2-4 weeks before starting a biologic as response after starting treatment can be poor.[22]

10.2. Live vaccines

The administration of live vaccines is contraindicated in patients on biologic agents and tofacitinib.[1,22]

It is safe to administer a live vaccine 4 weeks prior to commencing biologic therapy.

There is no contra-indication for the administration of live vaccines to relatives or friends of patients on biologic or immunosuppressant drugs with exception of infants exposed to treatment in utero. Vaccination of infants is discussed in section 9.8.

Table 4 shows current list of live vaccines available in the UK updated at the time of last review of this document. For up to date information consult the Green Book and BNF.

Table 4. List of live vaccines available in the UK[17, 24] (not to be used in patients on biologics)

Live vaccine	Brand name (where available)
BCG vaccine	Bacillus Calmette-Guerin vaccine (non-proprietary)
Live influenza vaccine	*Fluenz Tetra*® (nasal spray)
Measles, mumps and rubella (MMR) combined vaccine	*MMRvaxPRO®, Priorix®*
Rotavirus	*Rotarix®*
Typhoid vaccine	*Vivotif®*
Varicella-zoster (shingles) vaccine	*Zostavax®*
Varicella-zoster (chickenpox) vaccine	*Varilrix®, Varivax®*
Yellow fever vaccine	*Stamaril®*
Live (oral) poliomyelitis vaccine	No longer available for routine use

When a live vaccine is required by a patient on a biologic, it may be necessary to stop treatment with immunosuppressive treatment to enable safe administration. The table below shows the time period required to elapse for each biologic therapy, prior to the administration of a live vaccination.

Table 5. Time required for safe administration of live vaccine after last dose of biologic/tofacitinib[1,25]

Drug name	Time to elapse from last dose to administering live vaccine
Adalimumab	3 months
Golimumab	3 months
Infliximab	2 months
Ustekinumab	4 months
Vedolizumab	5 months
Tofacitinib	4 weeks

10.3. Non-live vaccines

Non-live vaccines are deemed safe to administer to people on immunosuppressant and on biologic therapies. Table 6 shows current list of live vaccines available in the UK updated at the time of last review of this document. For up to date information consult the Green Book and BNF.

Table 6. List of non-live vaccines available in the UK[22,24]

Live vaccine	Brand name (where available)
Cholera vaccine	*Dukural®*
Diphtheria – single-antigen vaccine not available; given as combination preparation containing other vaccines	Diphtheria with haemophilus influenzae type b, pertussis, poliomyelitis and tetanus - *Infanrix-IPV+Hib®* Diphtheria with pertussis, poliomyelitis and tetanus - *Boostrix-IPV®, Repevax®* Diphtheria with poliomyelitis and tetanus - *Revaxis®* Diphtheria with tetanus, pertussis, hepatitis B, poliomyelitis and haemophilus influenzae type b – *Infanrix Hexa®*
Haemophilus influenzae type B with meningococcal group C vaccine	*Menitorix®*
Hepatitis A vaccine	*Avaxim®, Havrix Monodose®, Vaqta®*
Hepatitis A with typhoid vaccine	*Viatim®*
Hepatitis B vaccine	*Engerix B®, Fendrix®, HBVAXPRO®*
Hepatitis A and B combined vaccine	*Ambirix®, Twinrix®*
Human papillomavirus vaccine	*Cervarix®, Gardasil®*
Influenza vaccine (non-live) NB New influenza virus strains circulate each year and therefore brands are developed seasonally.	*Agrippal®, Enzira®, Fluad®, Fluarix Tetra®, Imuvac®, Influenza MYL®, Influenza Tetra MYL®, Influvac® Sub-unit, Mastaflu®,* Influenza vaccine (non-proprietary) A list of the influenza vaccines available in the UK is published ahead of the influenza season in the national flu immunisation programme plan for England.
Meningococcal group B vaccine	*Bexsero® , Trumenba®*
Meningococcal group C vaccine	*NeisVac-C®*
Meningococcal polysaccharide A,C, W135 and Y vaccine (MenACWY)	*Menveo®, Nimenrix®*
Pneumococcal vaccine	*Pneumovax 23®, Prevenar® Synflorix®*
Poliomyelitis (non-live). Only in combined preparations.	See diphtheria section for combined preparations. Live oral poliomyelitis vaccine no longer in routine use.
Rabies	*Rabipur®,* rabies vaccine (non-proprietary)
Tetanus. Single preparation no longer available.	See diphtheria section.
Tick-borne encephalitis	*TicoVac®*
Typhoid vaccine	*Typherix®, Typhim Vi®;* also combined (see hepatitis A with typhoid vaccine)

11. Crohn's disease Severity Scoring and Clinical Monitoring

HARVEY BRADSHAW	SCORE	
GENERAL WELL-BEING		Please tick your score
Very well	0	☐
Slightly below par	1	☐
Poor	2	☐
Very poor	3	☐
Terrible	4	☐
ABDOMINAL PAIN *(yesterday)*		
None	0	☐
Mild	1	☐
Moderate	2	☐
Severe	3	☐
NUMBER OF LIQUID STOOLS *(yesterday)*		.....
ABDOMINAL MASS		
None	0	☐
Dubious	1	☐
Definite	2	☐
Definite and tender	3	☐
COMPLICATIONS	None	☐
Mouth ulcer ☐	Skin Rash	☐
Sore Joints ☐	Anal fissure	☐
Sore eyes ☐	Abscess	☐
Bruising on legs ☐	New fistula	☐

Remission	<5
Mild disease	5-7
Moderate disease	8-16
Severe disease	>16

Adapted from: http://www.janssenmedicalinformation.ca/assets/pdf/HarveyBradshaw_English.pd

12. Ulcerative Colitis Severity Scoring and Clinical Monitoring/ MAYO score

MAYO CRITERIA	SCORE	
STOOL FREQUENCY		**Please tick score**
Normal	**0**	□
1-2/day more than normal	**1**	□
3-4/day more than normal	**2**	□
≥ 5/day more than normal	**3**	□
RECTAL BLEEDING		
No blood seen	**0**	□
Streaks of blood with stool less than half the time.	**1**	□
Obvious blood with stool most of time.	**2**	□
Blood alone.	**3**	□
ENDOSCOPIC FINDINGS		
Normal or inactive disease	**0**	□
Mild disease (mild friability).	**1**	□
Moderate disease (Contact bleeding).	**2**	□
Severe disease (spontaneous bleeding).	**3**	□
PHYSICIAN'S GLOBAL ASSESSMENT		
Normal	**0**	□
Mild disease.	**1**	□
Moderate disease.	**2**	□
Severe disease.	**3**	□

The physician's Global Assessment acknowledges the Sub scores, the daily record of abdominal discomfort and functional assessment and other observations such as physical findings, and the patient's performance status

Full Mayo Index Score [sum of all above items]

Remission	≤2
Mild Disease	3-5
Moderate Disease	6-10
Severe Disease	11-12

Partial Mayo Index Score [sum of above items excluding endoscopic findings]

Remission =	0-1
Mild Disease	2-4
Moderate Disease	5-6
Severe Disease	7-9

Adapted from: Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987 Dec 24;317(26):1625-9.

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