High cost drugs pathways for inflammatory bowel disease in adults

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Review due 2 years from publication

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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
June 2020	RDTC	Updated to reflect most recent clinical guidance. Added NICE TA633 for ustekinumab in UC and subcutaneous infliximab formulation. Flowcharts updated	4.0
October 2021	Anna Pracz	Updated to reflect most recent clinical guidance. Added dose optimisation section including off-label escalation of infliximab.	4.1.
November 2021	Anna Pracz	Updated to include DSU for tofacitinib and clarify changes to IFR approval route, following MGSG	4.2
January 2022	Anna Pracz	Changes to chapter 6	4.3
June 2022	Anna Pracz	Alignment with existing pathways – review of the non-clinical parts of pathway; addition of filgotinib to treat UC	4.4
June 2023	Anna Pracz	Further alignment with GM high cost drugs pathway. Update to algorithms and clinical content as per national guidance. Incorporation of ECCO guidance on fertility and pregnancy.	4.5a
September 2023	Anna Pracz	Final review following consultation comments (minor corrections)	4.8

Approvals

This document must be approved by the following before distribution:

NAME	DATE OF ISSUE	VERSION
IBD working group	03.07.23	4.6 final draft
Clinical Reference Subgroup – for consultation	11.07.23	4.7 (minor changes)
Clinical Reference Subgroup – post consultation	12.09.23	4.8
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High cost drugs pathways for inflammatory bowel disease in adults

1. Background

These pathways are intended as guidelines in the initiation and maintenance of high cost drugs in the management of inflammatory bowel disease (IBD) in adults, including ulcerative colitis (UC) and Crohn's disease (CD). The pathways have been written using up to date published research and evidenced based medicine. This originated as a clinical project implemented by Manchester Academic Health Science Centre (MAHSC), a joint project between the gastroenterology departments of the Greater Manchester hospital trusts.

Currently the pathways include following classes of high cost drugs:

- biologic agents (biologics, biologicals)
  - tumour necrosis factor inhibitors (anti-TNFs; infliximab, adalimumab and golimumab)
  - integrin inhibitor (vedolizumab),
  - interleukin inhibitors (risankizumab, ustekinumab)
- targeted synthetic agents (small molecules)
  - Janus kinase inhibitors (JAKi; tofacitinib, filgotinib, and upadacitinib)
  - sphingosine 1-phosphate (S1P) receptor modulator (ozanimod)

2. NICE guidance

Biological therapies and small molecule agents are indicated when a patient's disease has an inadequate response to conventional treatments*, or these options are contraindicated or not tolerated.

Links to relevant NICE guidelines and technology appraisals (TA) are listed below. The NICE recommendations also apply to biosimilar products of the technologies that have a marketing authorisation, allowing the use of the biosimilar for the indication specified in the relevant NICE TA.

Any new high cost drugs that receive positive recommendation from NICE between this document iterations are approved for routine use within criteria specified in NICE technology appraisal and will be included in upcoming pathway updates.

2.1. Crohn's disease

Please see links below for full NICE guidance.

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

- NICE TA187 (2010): Infliximab and adalimumab for the treatment of Crohn's disease
- NICE TA352 (2015): Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy
- NICE TA456 (2017): Ustekinumab to treat moderately to severe Crohn's disease after previous treatment
- NICE TA888 (2023): Risankizumab for previously treated moderately to severely active Crohn's disease
- NICE TA905 (2023): Upadacitinib for previously treated moderately to severely active Crohn's disease

2.2. Ulcerative colitis

Please see links below for full NICE guidance.

NICE (2019): Ulcerative colitis: management NG130

- NICE TA329 (2015): Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy
- NICE TA163 (2008): Infliximab for acute exacerbations of ulcerative colitis
- NICE TA342 (2015): Vedolizumab for treating moderately to severely active ulcerative colitis

* For the purpose of this guideline conventional treatment include well-established traditional treatments such as 5-aminosalicylates [5-ASA], corticosteroids, and thiopurine immunomodulators. (9)

- NICE TA547 (2018): Tofacitinib for moderately to servery active ulcerative colitis
- NICE TA633 (2020): Ustekinumab for treating moderately to severely active ulcerative colitis
- NICE TA792 (2022): Filgotinib for treating moderately to severely active ulcerative colitis
- NICE TA828 (2022): Ozanimod for treating moderately to severely active ulcerative colitis
- NICE TA856 (2023): Upadacitinib for treating moderately to severely active ulcerative colitis

3. Initiating treatment with a high cost drug

All NICE-approved high cost drugs for treatment of inflammatory bowel disease are routinely commissioned if prescribed in accordance with this pathway and used in line with criteria laid out in the relevant NICE technology appraisal. This includes any new high cost drugs that are approved by NICE between pathway revisions.

The choice of treatment should be guided by clinical judgement, national and local guidance, and the overall value proposition offered by the individual medicines. There are numerous factors which may influence the choice of drug at each point in the pathway, including disease presentation, extra-intestinal presentation, co-morbidities, dexterity, previous treatment history and adherence, dexterity, route of administration, frequency, devices available. These factors should be considered in a discussion between the patient and their clinician, including the advantages and disadvantages of the treatments available. The rationale for choice should be documented.

Patients with other concomitant inflammatory disorders (e.g. psoriasis or inflammatory arthritis) may benefit from a drug that is also indicated for this comorbidity and approved under the appropriate GMMMG High Cost Drugs Pathway.

If more than one treatment is suitable, the best value product should be chosen (taking into account price per dose, dosage and treatment frequency and administration costs and biosimilar availability). At the time of this version publication this was biosimilar adalimumab. Clinicians should also contact pharmacy for advice on the relative cost of these drugs. If the least expensive product is not prescribed, the reasons why must be documented made available to commissioners if requested. Records can be made on Blueteq forms where available.

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. See section 12 for more on registries.

Treatment should be reviewed to assess efficacy as per NICE guidance, and thereafter at least every 12 months. For treatment pathways, see flowcharts in sections 14 and 15.

4. Biosimilars

Use of biosimilars, including switching from originator to a biosimilar, has become routine clinical practice. All NICE guidance on biologics applies to biosimilar medicines. The MHRA advises that (1):

- Once authorised, a biosimilar product is considered to be interchangeable with their reference product (originator), which means a prescriber can choose the biosimilar medicine over the originator (or vice versa) and expect to achieve the same therapeutic effect. Likewise, a biosimilar product is considered to be interchangeable with another biosimilar to the same reference product.
- As a result of interchangeability, switching patients from one product to another (originator or biosimilar) has become routine clinical practice. The decision rests with the prescriber in consultation with the patient, in line with the principles of shared decision making; both need to be aware of the brand name of the product received.
- All biological medicines, including biosimilars, should be prescribed by brand name to support on-going pharmacovigilance of the individual products. (2)

Further, the British Society of Gastroenterology (BSG) advises that automatic substitution is inappropriate (at point of dispensing).

N.B. Inflectra and Remsima are different brands of infliximab and are marketed by different companies, but it should be noted that they are the same biosimilar (CPT-13, produced by Celltrion).

5. Alternative dosing of high cost drugs (including dose escalation and de-escalation)

Treatment optimisation, including dose escalation, and de-escalation, is licensed for several drugs, although dosing adjustment is not recommended for newer subcutaneous formulations of infliximab and vedolizumab.

For treatment initiation refer to individual drug's SPC via https://www.medicines.org.uk/.

For some drugs, reduced doses are indicated in the elderly, renal impairment, hepatic impairment and according to blood test results – see section 23 for specific monitoring considerations and summary of product characteristics for adjusted dosing. For safety alerts recommending dose adjustments see section 23.

Patients with other concomitant inflammatory disorders may benefit from dose escalation, where recommended by manufacturer or supported by other clinical evidence; see other relevant GMMMG High Cost Drugs pathways for more information.

Off-label escalation of infliximab is now a routine clinical practice in GM. See sections 8 and 14 for guidance on anti-TNF dose adjustment following poor or loss of response.

Table 1. Standard and alternative HCD regimens

Drug	**Standard maintenance dose** (3)	**Alternative regimes** (3) (4)	
		Crohn's disease	**Ulcerative colitis**
Adalimumab (SC)	40 mg every 2 weeks	40 mg every week, or 80 mg every 2 weeks	
Filgotinib (PO)	200mg daily	Not licensed in Crohn's disease	Not specified in the marketing authorisation
Infliximab (IV)	5 mg/kg every 8 weeks	If response poor or lost *5 mg/kg every 6 weeks* or *5mg/kg every 4 weeks* or 10mg/kg every 8 weeks or *10mg/kg every 6 weeks* or *10mg/kg every 4 weeks*	If response poor or lost *5 mg/kg every 6 weeks* or *5mg/kg every 4 weeks* or *10mg/kg every 8 weeks* or *10mg/kg every 6 weeks* or *10mg/kg every 4 weeks*
Infliximab (SC)	120mg every 2 weeks	Not specified in the marketing authorisation	
Golimumab (SC)	Ulcerative colitis only: 50 mg every 4 weeks or 100 mg every 4 weeks if body weight ≥80 kg	Not licensed in Crohn's disease	100 mg every 4 weeks, if inadequate response at week 6 or body weight ≥80 kg
Ozanimod (PO)	0.92mg once daily	Not licensed in Crohn's disease	Not specified in the marketing authorisation
Risankizumab	Crohn's disease only: 360mg every 8 weeks	Not specified in the marketing authorisation	Not licensed in ulcerative colitis
Tofacitinib (PO)	Ulcerative colitis only: 5 mg twice daily	Not licensed in Crohn's disease	10 mg BD for an additional 8 weeks, followed by 5 mg BD, if adequate response not achieved in first 8 weeks
Upadacitinib (PO)	15 or 30 mg once daily based on individual patient presentation	Not included in the marketing authorisation	Not included in the marketing authorisation
Ustekinumab (SC)	90 mg every 12 weeks	90 mg every 8 weeks, if response lost with dosing every 12 weeks **NB escalation off-label is not routinely commissioned – see** GMMMG (2023) Off-label ustekinumab regimens for inflammatory bowel disease including Crohn's disease and ulcerative colitis	
Vedolizumab (IV)	300 mg every 8 weeks	300 mg every 4 weeks, if response lost with dosing every 8 weeks	
Vedolizumab (SC)	108 mg every 2 weeks	Not included in the marketing authorisation	

IV – intravenous; PO - oral; SC – subcutaneous *off-label regimens in italics*

Patients who are in stable clinical remission should be considered for a trial withdrawal of therapy.

6. Treatment failure

The available guidance recommends considering changing to an alternative high cost drug if treatment fails due to inefficacy or adverse events. For the purposes of this pathway, this can include failure due to inefficacy:

- Primary failure: disease does not respond adequately to a high cost drug within the timescales defined in the marketing authorisation and NICE technology appraisal (see sections 2 and table 2 in section 13)
- Secondary failure: disease initially responds adequately within the timescales defined in marketing authorisation and NICE technology appraisal (see section 2), but the patient subsequently loses this response. Although all high cost drugs are highly efficacious in the short term, longer-term attrition is expected. In effect, changes to therapy are likely to be required for longer term disease control for a life-long condition.

There may be other reasons for treatment discontinuation, including:

- adverse effects resulting in reduced tolerability
- newly identified drug safety issue during successful treatment resulting in a newly identified contraindication
- patient becoming pregnant (see section 20.2)

7. Sequential use of high cost drugs

Prior to switching to a subsequent treatment, consideration should be given to dose escalation where there is evidence to support safety and efficacy (see section 5), and when an inadequate primary response may be due to insufficient drug dosing. For example, in obese patients or when disease relapses during the treatment cycle.

Degree of response or lack of response to one high cost drug is not directly predictive of a patient's likely response to alternative agents in an alternative class, or even in the same class and depends on several factors including type of loss of response and clinical context. (5; 6)

High cost drugs for inflammatory bowel disease currently have several different molecular targets (e.g., TNFα, IL-12/23, JAK proteins), or have varying affinity or avidity where the target is the same. Using an agent with a different mechanism of action to the failed therapy may result in regaining disease control. (6)

Choice of subsequent agent should be made following review by a specialist with consideration given to the mechanism of action of previously used drugs, the severity and current level of disease control, the presence of co-existing conditions, as well as the patient's past medical history and with regards to contraindications and precautions to available treatment options. This should be a shared decision with the patient. See section 3 for more details on factors to consider when initiating treatment with a new high cost drug.

In complex cases, it is recommended to seek advice from other professional colleagues, e.g. as a part of multi-disciplinary team discussion. Where available, a specialist pharmacist should be involved in decision making. With each new treatment, patients must meet the criteria laid out in the relevant NICE technology appraisal or otherwise stipulated in this pathway. There is no need for an individual funding request in such circumstances.

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 clinical circumstances of individual patient should be considered in each case to aid decision making. Drug levels and half-lives of drugs included in this pathway (listed in table 3) may also be considered, if appropriate.

Switching to a biosimilar of successful treatment (e.g. as a part of switching programme) is not considered a sequential high cost drug use.

Repeated pre-high cost drug checks should be considered when switching to a new agent as per clinical judgement, and depending on the duration of previous therapy, the clinical picture of individual patient and relevant risk factors.

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

The pathways include three tumour necrosis factor-alpha inhibitors (anti-TNFs): infliximab, adalimumab and golimumab. Failure to respond and loss of clinical effect to anti-TNF therapy are both common in gastroenterology patients. (7; 8)

There is limited data for the use of drug level monitoring during induction to guide therapy (6) and the evidence is currently insufficient to recommend for or against the use of reactive therapeutic drug monitoring to improve clinical outcomes. (9; 10) Measuring drug and antibody levels early in primary non-responders and when secondary loss of response occurs may provide information to guide clinical decision making. (10) As a biologic therapy optimisation initiative, proactive therapeutic drug monitoring (TDM) (i.e. where there is no loss of response) can provide evidence for the need for continued anti-TNF therapy in individual patients and give reassurance to patients following a switch to biosimilar via demonstrable evidence of unaltered drug efficacy.

Currently, TDM and antibody testing in IBD patients is available for infliximab and adalimumab. 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.

At the time of writing, guidance relating to antibodies and drug levels for golimumab and biologics with different mechanisms of action (ustekinumab and vedolizumab) was not available.

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

9. Data collection requirements

Patient-level information including full clinical details, e.g. disease scores at treatment initiation and assessment for continuation, previous drug history, reasons for change of treatment must be made available to commissioners. This is expected to be via Blueteq, where commissioned.

Where available and subject to contractual arrangements Blueteq forms which comply with this pathway should be filled in for each new high cost drug at initiation and continuation to secure funding.

Where agreed, data available from Blueteq system or clinical audit may be used to monitor compliance with NICE and GMMMG pathway and for other purposes (e.g. service development or pathway extension for newly identified cohorts of patients).

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

10. Individual funding requests (IFR)

Individual funding requests will be considered under the GM EUR Operational Policy.pdf (gmeurnhs.co.uk).

Exhausting the treatment options in this pathway does not automatically establish exceptionality.

11. Free of charge schemes

All free of charge schemes must be approved in accordance with trust guidance and the GMMMG Free of Charge guidance. (11) Approval should be agreed at the trust's medicines management committee.

There must be clear exit criteria that do not place financial burden on commissioners and do not raise patients' expectations of continuation of treatment.

12. Research

Where available, enrolment in a suitable registry or observational clinical trial is encouraged so that specific information about these treatments in inflammatory bowel disease can be captured.

Clinicians are strongly encouraged to participate in long-term safety studies or registries such as the IBD Registry. For more information visit https://ibdregistry.org.uk/about-us/ .

Some sites host early and later phase clinical trials of novel high cost drugs. Active trials can be found on the NIHR website.

13. Available drugs and factors affecting drug choice

Where multiple treatment options are clinically suitable the best value drug, all factors considered, should be chosen. See section 3 for considerations regarding new drugs initiation. Consider oral or intravenous options if needle phobia or inability to self-administer subcutaneous injections; intravenous preparations may help address adherence issues, or severely impaired manual dexterity. Note that all biologics and small molecule therapies may increase infection risk, particularly in those who remain steroid-dependent and on immunomodulators.

For safety alerts on safety of JAK inhibitors see section 16.2.

Anti-TNFs should be given in combination with a thiopurine or methotrexate (only for CD) if thiopurines are contraindicated as evidence demonstrates improved outcomes in comparison with monotherapy, partially due to reduced risk of immunogenicity. (12)

Currently there is no evidence to support combined therapy for ustekinumab, vedolizumab, JAK inhibitors and ozanimod.

Table 2. Available HCDs – information to support choice

Drug	Mode of action	Route	Licence (CD/UC)	Max time to response time (3)	Factors affecting drug choice
Adalimumab	TNF-inhibitor	SC	CD & UC	CD: 4-12 weeks UC: 2-8 weeks	NICE-approved in psoriasis (TA146), rheumatoid arthritis (TA195 and TA715), psoriatic arthritis (TA199), ankylosing spondylitis (TA383), juvenile idiopathic arthritis (TA373), hidradenitis suppurativa (TA392), uveitis (TA460) Rapid loading possible for CD
Golimumab	TNF-inhibitor	SC	UC	12-14 weeks after starting treatment (after 4 doses)	NICE-approved in rheumatoid arthritis, psoriatic arthritis (TA220), ankylosing spondylitis Consider for use in patients weighing >80kg (higher dose licensed in this population).
Infliximab	TNF-inhibitor	IV & SC	CD & UC	CD: 6 weeks (after 2 doses) Fistulating CD: 3 doses UC: 14 weeks (after 3 doses)	**Indicated for active fistulising CD** NICE-approved in psoriasis (TA134), psoriatic arthritis (TA199), ankylosing spondylitis (TA383), rheumatoid arthritis (TA195 and TA715) Some evidence for efficacy in uveitis (but no licence) (13)
Filgotinib	JAK inhibitor	PO	UC	10-22 weeks	NICE-approved in rheumatoid arthritis (TA676)
Ozanimod	S1-receptor modulator	PO	UC	SPC does not specify; 10 weeks in pivotal clinical trial	NICE-approved in multiple sclerosis (TA706) 7 days of up-titration needed during initiation
Risankizumab	IL-23 inhibitor (p19)	IV then SC	CD	12-24 week*	NICE-approved in psoriasis (TA596) and psoriatic arthritis (TA803) May be used first line in elderly patients or close contacts of patients with TB, previous malignancy
Tofacitinib	JAK inhibitor	PO	UC	8-16 weeks	NICE-approved in psoriatic arthritis (TA543) and rheumatoid arthritis
Upadacitinib	JAK inhibitor	PO	CD & UC	CD: 12-24 weeks UC: 8-16 weeks	NICE-approved in moderate and severe rheumatoid arthritis (TA665) and TA744), psoriatic arthritis (TA768), radiographic ankylosing spondylitis (TA829) and non-radiographic axial spondyloarthritis (TA861)
Ustekinumab	IL-12/23 inhibitor(p40)	IV then SC	CD & UC	CD&UC: 16 weeks after the IV induction or 16 weeks after switching to the SC formulation (2 SC doses)	NICE-approved in psoriasis (TA180), and psoriatic arthritis (TA340) May be used first line in elderly patients or close contacts of patients with TB, previous malignancy
Vedolizumab	Integrin inhibitor	IV & SC	CD & UC	CD: 10-14 weeks UC: 10 weeks	May be used first line in elderly patients or close contacts of patients with TB, previous malignancy

* as suggested by manufacturer

14.GM HCD Pathway for IBD – Crohn's disease

Moderate to severe active disease despite optimal therapy with conventional agents as per NICE NG129

At all stages when treating with HCD
- Consider entry to a registry and a clinical trial (where criteria are met)
- Review applicable patient, disease, and drug factors, e.g., dexterity, adherence, comorbidities, weight, drug history, family planning, risk of infection, route of administration, device, and dose frequency.
- See section 22 for drug specific screening questions for pre-admission

First line (HCD-naive): choose based on clinical factors and best value. For more details see table 2 and purple box in bottom right corner.

NICE NG129: *Therapy should be given as a planned course until treatment failure (including the need for surgery) or until 12 months after starting, whichever is shorter.*

Assess response at 6-16 weeks (see table 2 and drug SPCs)
- Clinical response (e.g. HBI)
- Bloods (e.g. CRP, albumin) ± faecal calprotectin (FCP)

Good clinical response

(i.e. reduction in clinical score, e.g. HBI; CRP & FCP)

Continue scheduled prescribing and clinical review

Partial or poor response

Optimise HCD and immunosuppressant (if relevant)
- If on anti-TNF and possible to dose-optimise based on TDM, assess response after 4-8 weeks; repeat cycle max 2x
- If on non-anti TNF – optimise as per SPC and table 1

Primary failure

Criteria for response not met within timescales defined by NICE. i.e. no clinical response to initial therapy

(Re)assess response at 12 months since start of treatment to determine whether ongoing treatment is still clinically appropriate (NICE review). Discuss at MDT, where available.
- Clinical symptoms and response (e.g. HBI)
- Biological markers: bloods ± faecal calprotectin
- Investigation, including endoscopy, if necessary

Secondary non-response (loss of response)

Remission (i.e. asymptomatic, with biochemical and/or endoscopic and/or radiological evidence of healing)
- Consider stopping biologic/dose tapering + maintaining immunosuppressant **[BSG, 2019]**
- Restart treatment if patient relapses after treatment is stopped

Ongoing disease (i.e. clear evidence of ongoing active disease, determined by clinical symptoms, biological markers and/or investigation)
- Optimise HCD – as per SPC and table 1
- If appropriate, move to next step in treatment pathway if response is lost at any point during therapy

Active fistulating disease - Infliximab IV or SC (TA 187)

Confirming active IBD flare
- Calprotectin
- Bloods (routine; anti-TNF ADAb and drug levels)
- Endoscopy / radiology
- Exclude alternative pathology – e.g. stricture, cancer, infection, IBS

Therapeutic drug monitoring TDM (adalimumab/infliximab)
- Target adalimumab drug trough level ≥ 5 mcg/mL (suggest aim: 5-10 mcg/mL)
- Target infliximab drug trough level = 7-10 mcg/mL
- Note results can vary depending on assay and centre used for analysis

Drug levels low/ undetectable and ADAb-ve
- ➢ Check adherence
- ➢ Increase drug dose or frequency
- ➢ Add in or optimise immunosuppressant

Drug levels low/ undetectable and ADAb +ve

Potential loss of response
- ➢ Add in immunosuppressant
- ➢ Switch to another anti-TNF*
- ➢ Swap to non-anti TNF or non-biologic

Drug level within or above range/ADAb +/-ve and clinical loss of response

Likely non-TNF-driven disease. Switch to:
- ➢ non-anti TNF
- ➢ non-biologic

*Consider appropriate alternative (if ADAb levels allow)

Anti-TNF drug level & antibodies undetectable – assess adherence, increase drug dose and frequency if appropriate – see table 1. Consider BMI: is dose weight-adjusted? If adjustments do not result in adequate response, consider switching to alternative bDMARD or JAK inhibitor. See table 2 for choice.

- **Consider entry to a trial**
- **Consider surgery**
- **Consider an alternative HCD**

Consider patient and disease factors, previously used drugs and their mode of action, drug levels and antibody levels (where relevant), immunogenicity. See purple box and table 2 for choice.

purple box and table 2 for choice.

See section 20 for patient screening questions for HCD initiation

Choice of HCD for Crohn's disease (also see table 2)

Anti-TNFs (1st choice)
- adalimumab
- infliximab

If anti-TNFs not suitable or not tolerated:
- ➢ **Non-anti-TNF biologics**
- ustekinumab
- risankizumab
- vedolizumab, or
- ➢ **JAKI inhibitor:**
- upadacitinib

Allowed dose escalations – see table 1

15. GM HCD Pathway for IBD – Ulcerative colitis

Moderate to severe active disease despite optimal therapy with conventional agents as per NICE NG130

At all stages when treating with HCD
- Consider entry to a registry and a clinical trial (where criteria are met)
- Review applicable patient, disease, and drug factors, e.g., dexterity, adherence, comorbidities, weight, drug history, family planning, risk of infection, route of administration, device, and dose frequency.
- See section 22 for drug specific screening questions for pre-admission

First line (HCD-naive): choose based on clinical factors and best value. For more details see table 2 and purple box to the right.

NICE NG130: *Therapy should be given as a planned course until treatment failure (including the need for surgery) or until 12 months after starting, whichever is shorter.*

Assess response at 6-16 weeks (see drug SPCs and table 2)
- Clinical response (e.g. UCDAI, Mayo score)
- Bloods ± faecal calprotectin

Good clinical response, i.e.
- Clinical response (e.g. UCDAI, Mayo score), lab markers (CRP, faecal calprotectin), and investigations

Partial or poor response

Optimise HCD and immunosuppressant (if relevant)
- If on anti-TNF and possible to dose-optimise based on TDM, assess response after 4-8 weeks; repeat cycle max 2x
- If on non-anti TNF – optimise as per manufacturers recommendations (table 1)

Primary failure
Criteria for response not met within timescales defined by NICE, i.e. no clinical response to initial therapy

Reassess response at 12 months since start of treatment to determine whether ongoing treatment is still clinically appropriate (NICE review). Discuss at MDT, where available.
- Colonoscopy/sigmoidoscopy
- Biological markers: bloods ± faecal calprotectin
- Clinical symptoms and response, e.g. Mayo score, UCDAI)

Remission (i.e. asymptomatic, with biochemical and/or endoscopic and/or radiological evidence of healing)
- Consider stopping biologic/dose tapering + maintaining immunosuppressant **[BSG, 2019]**
- Restart treatment if patient relapses after treatment is stopped

Ongoing disease (i.e. clear evidence of ongoing active disease, determined by clinical symptoms, biological markers and/or investigation)
- Optimise HCD – as per SPC and table 1
- If appropriate, move to next step in treatment pathway if response is lost at any point during therapy

Secondary non-response (loss of response)

- **Consider entry to a trial**
- **Consider surgery**
- **Consider an alternative HCD**

Consider patient and disease factors, previously used drugs and their mode of action, drug levels and antibody levels (where relevant), immunogenicity. See purple box and table 2 for choice.

See section 22 for patient screening questions for HCD initiation

Acute exacerbation of severely active UC

Infliximab IV 5mg/kg (TA 163)
Unless ciclosporin is considered more clinically appropriate

Assess response daily
Consider extra 5mg/kg infliximab if no clinical benefit and extensive haemorrhage colitis

Clinical response
Complete loading of infliximab and commence maintenance [Ref BSG, 2019].

Wean steroids, commence oral immunosuppression

Poor response

Consider colectomy
Benefits of switching between ciclosporin and infliximab if one fails are not clear (7)

Ciclosporin (IV) 2mg/kg / 24 hrs
Consider if infliximab has previously failed or bridging therapy required to a biologic with long response time (e.g. vedolizumab)

Assess response daily

Clinical response
Start oral immunosuppression and antimicrobial (if indicated) **or** commence switch to biologic (when ciclosporin used as bridging therapy)

Choice of HCD for ulcerative colitis (also see table 2)

Anti TNFs
- adalimumab (1st choice)
- infliximab (1st choice)
- golimumab

If anti-TNFs not suitable or not tolerated
- ➢ **non-anti-TNF biologics**
- ustekinumab
- vedolizumab
- ➢ **JAKIs**
- filgotinib
- tofacitinib
- upadacitinib
- ➢ **S1PI**
- ozanimod

For therapeutic drug monitoring TDM (adalimumab/infliximab)
➢ **see previous page (section 14)**

Allowed dose escalations – see table 1

16. Contraindications, special warnings and precautions for treatment with drugs

16.1. Cautions and contraindications

Cautions, contraindications, and special warnings to use of systemic agents for IBD are detailed in the individual summaries of products characteristics (SPCs), which are available from www.medicines.org.uk. (3) Prescribers should consult the relevant SPC to inform clinical decision-making for individual patients.

It is important that clinical teams regularly identify patient cohorts affected by new and existing safety alerts. Review of appropriateness of continuing or changing treatment should be assessed on case-by-case basis and allowing shared decision making.

16.2. Additional safety considerations

The MHRA has published Drug Safety Updates relating to several of the drugs included in this pathway, all of which are available from www.gov.uk/drug-safety-update:

- Janus kinase (JAK) inhibitors: new measures to reduce risks of major cardiovascular events, malignancy, venous thromboembolism, serious infections, and increased mortality (2023).
  In clinical trials of patients with RA, an increased incidence of malignancy, major adverse cardiovascular events (MACE), serious infections, venous thromboembolism (VTE) and mortality, was observed in patients treated with some JAK inhibitors, particularly tofacitinib, when compared to those treated with anti-TNFs.
  - It is advised to avoid prescribing JAK inhibitors unless there are no suitable alternatives in patients with the following risk factors: age 65 or older, current or past long-term smoking and other risk factors for cardiovascular disease or malignancy.
  - JAK inhibitors should be used in caution if prescribing in patient with any risk factors for VTE. Lower doses should be use where specified the individual summaries of product characteristics.
  - Incidence of non-melanoma skin cancer was higher in tofacitinib trials when compared with anti-TNFs. Therefore, periodic skin examinations for signs of skin malignancy is recommended in all patients on JAK inhibitors. Inform patients of these risks and key signs and symptoms that could warrant urgent medical attention.

  As indicated in 14.1, appropriateness of continuing or changing treatment in the context of the above guidance should be assessed on a case-by-case basis and with shared decision making.

- Tofacitinib (Xeljanz▼): new measures to minimise risk of major adverse cardiovascular events and malignancies, October 2021. Tofacitinib should not be used in patients older than 65 years of age, people who are current or past smokers, or individuals with other cardiovascular risk (such as diabetes or coronary artery disease) or malignancy risk factors unless there are no suitable alternative treatments.
- Tofacitinib (Xeljanz▼): new measures to minimise risk of venous thromboembolism and of serious and fatal infections; March 2020. Maintenance treatment for ulcerative colitis at the 10mg twice-daily dose is not recommended in patients with known risk factors for venous thromboembolism unless there is no suitable alternative treatment. Due to risk of serious and fatal infections, healthcare professionals are advised only to use tofacitinib in patients older than age 65 years if there is no alternative treatment.
- Live attenuated vaccines: avoid use in those who are clinically immunosuppressed; April 2016
- Ustekinumab (Stelara): risk of exfoliative dermatitis; January 2015. Be alert for signs and symptoms of exfoliative dermatitis or erythrodermic psoriasis. Start appropriate treatment promptly if these occur and stop ustekinumab if exfoliative dermatitis is suspected to be an adverse reaction to ustekinumab.
- Tumour necrosis factor alpha inhibitors; December 2014. Risk of tuberculosis - screen all patients before starting treatment and monitor them closely.

16.3. Malignancy

The use of high cost drugs in patients with a history of malignancy should involve a detailed discussion with the patient around the risks and benefits of treatment and consideration should be given to involving their oncologist. If a cancer occurs during treatment with a high cost drug, oncologist advice on treatment should be sought.

17. Pre-high cost drug screening

Please refer to the checklist provided at the end of the document (section 22), which can be adapted locally if necessary.

17.1. Tuberculosis (TB)

Interferon gamma (gIFN) testing is recommended prior to commencing biologic/JAK treatment if available. Parts of Greater Manchester are identified as areas of high-risk for tuberculosis. In patients with high index of suspicion or risk of tuberculosis consider referring to previously published algorithms for additional screening (14) and referral for a respiratory opinion if deemed necessary: See NICE guideline NG33, Tuberculosis (Sept 2019), for further information.

17.2. Hepatitis B & C

Screening for hepatitis B and C is recommended for all patients starting a biologic and JAK inhibitors. Screening should include: (15)

- Hepatitis B: screen for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc, HBcAb), followed by HBV DNA test if HBsAg or anti-HBc are positive.
- Hepatitis C: screen for anti-hepatitis C antibodies. If test is positive, hepatitis C RNA or core antigen assays should be performed.

If either hepatitis B or hepatitis C infection is suspected, discuss with a hepatologist. Treatment with a biologic may be appropriate but should follow a risk/benefit decision made with a hepatologist, infectious disease or another relevant specialist.

17.3. Human immunodeficiency virus (HIV)

Screening for HIV is recommended for all patients starting a biologic/JAK. NICE Quality Standard QS157 (Sept 2017) recommends young people and adults are offered an HIV test when admitted to hospital in areas of extremely high HIV prevalence, or when having a blood test when admitted to hospital in areas of high HIV prevalence. Greater Manchester is an area of high and extremely high HIV prevalence. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults recommends risk factors for HIV infection should be documented prior to commencing a biologic and, if present, an HIV test should be performed. If considering the use of biologic/JAK therapy in HIV positive patients, this should be discussed with an HIV specialist.

18. Special considerations – very severe disease

18.1. Poor prognostic factors in Crohn's disease

The course of Crohn's disease may be predicted by clinical factors at diagnosis and/ or at endoscopy. Aggressive Crohn's disease is characterised by features such as increased relapse rates, and hospital admissions, the development of penetrating or stricturing disease, abscesses, or the need for surgery. (16)

Factors which may suggest a poor prognosis include (17; 18; 19)

- early onset and early recurrence (i.e. age under 40 at diagnosis)
- severe symptoms at presentation
- perianal/ rectal disease
- requirement of corticosteroid at diagnosis
- a history of two or more surgical resections or early recurrence
- deep and extensive colonic ulceration
- complex disease, e.g. abscesses, strictures, fistulas, or penetration; steroid dependency or inability to use steroids as bridge to immunosuppression, patients already on immunosuppression

The treating specialist could consider early introduction of high cost drug therapy in those with extensive disease or other poor prognostic features including those listed above. (6) The decision to initiate early treatment with HCD should also consider factors such as impact on work or other activities of daily living, and availability of other treatment options. (6)

Other factors which can have adverse impact on Crohn's disease and treatment outcomes are:

- Unintentional weight loss pre-diagnosis (more than 5kg pre-diagnosis), or low body mass index

- Smoking - (including light or passive smoking which carries equal risk as heavy smoking). Smokers should be encouraged to stop.
- Obesity - it can be argued that obesity can contribute to poorer outcomes of treatment with biologics, in particular anti-TNFs (20; 21), and impacts on overall risk of surgical interventions.

18.2. 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. (22) In patients with extensive haemorrhagic colitis who have not responded to initial treatment, a higher dose of infliximab (10 mg/kg loading, or a second 5 mg/kg after 3-5 days, both unlicensed) can be considered at the discretion of the clinician in order to reduce the risk of colectomy. (22; 23) This would be an immediate rescue treatment and not an individual funding request.

19. Surgery and perioperative risk

Risk of postoperative infection may be reduced by temporarily stopping treatment with a biologic or JAK inhibitor. The safe interval remains to be determined. BSG advise to optimise dose of immunomodulators and biologics prior to and after surgery as part of the IBD operative checklist. (6) 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 (3) (see table below). Biologic and JAK-inhibitor therapy should not delay urgent surgery.

Table 3. Peri-operative supportive information (3; 24)

Drug	Dosing interval	Period in which surgery should be scheduled (relative to last drug dose administered)	One mean half-life	Five half-lives
Adalimumab SC	Every 2 weeks	Week 3	14 days	70 days
Filgotinib PO	Once daily	Day 5*	19 hours	4 days
Golimumab SC	Every 4 weeks	Week 5	14 days	70 days
Infliximab IV	Every 4, 6 or 8 weeks	Week 5, 7 or 9	9 days	45 days
Infliximab SC	Every 2 weeks	Week 3**	14 days	70 days
Infliximab SC	Every 2 weeks	Week 3	14 days	70 days
Ozanimod PO	Once daily	Week 1***	21 hours	5 days
Tofacitinib PO	Twice daily	Day 7*	3 hours	15 hours
Ustekinumab IV/SC	Every 8 or 12 weeks	Week 9 or 13	21 days	105 days
Upadacitinib PO	Once daily	Day 4*	14 hours	3 days
Vedolizumab IV	Every 4, 6 or 8 weeks	Week 5, 7 or 9	24 days	119 days
Vedolizumab SC	Every 2 weeks	Week 5	26 days	130 days

* Tofacitinib is rapidly eliminated but treatment effects do not reverse fully within 2 weeks after discontinuation, indicating a longer duration of pharmacodynamic activity compared to the half-life (3). Although not stated in summary of product characteristics this may be applicable to all JAK inhibitors due to mechanism of action. Prescribers may wish to consider longer time to surgery, i.e. Week 2.

**No published guidance available, recommendation based on half-life (3) or dosing interval.

*** No published guidance. Ozanimod's half-life is 21hrs, however half-life of its active metabolite is 11 days. Prescribers may wish to consider longer time to surgery.

19.1.1. Postoperative recurrence of Crohn's disease

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, provided NICE criteria for use are met (see section 2). 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. (25)

20. Fertility, pregnancy, and conception

Prescribers should be mindful that evidence base evolves and to use the most up to date national guidance if in doubt. At the time of writing, the European Crohn's and Colitis Guidelines on Sexuality, Fertility, Pregnancy, and Lactation published in 2023 was based on most up to date evidence and should be referred to in first instance. Where data is not available (e.g. for newer drugs), manufacturers' recommendations may be taken into consideration.

20.1. Fertility and conception

Medicines included in this pathway may affect fertility and conception. Women of childbearing potential should use effective contraception during treatment and continue use for the number of weeks after treatment has stopped unless this is advised as not necessary, e.g. for anti-TNFs (see section 20.2 and table 4 within). Paternal exposure to most high cost drugs included in this pathway is compatible with pregnancy. For details, refer to ECCO 2023 guideline or other most up to date clinical guidance.

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.

20.2. Pregnancy

ECCO's pregnancy and IBD algorithm can be accessed here. The ECCO 2023 guideline include the following statements:

- Achieving clinical remission may increase the probability of successful conception. Active disease is also associated with decreased fertility in men with IBD.
- Pregnancy may increase the risk of relapse or worsening disease in patients with UC and complications in patients with CD, especially if disease is active at conception. IBD remission before conception is recommended.
- JAK inhibitors and S1P receptor modulators should be avoided during pregnancy. Where planning pregnancy, stop JAKIs and ozanimod before conception, and consider alternative therapy to ensure good disease control.
- For women in remission, discontinuing anti-TNF prior to the third trimester is not recommended, as it may increase the risk of relapse and lead to unfavourable pregnancy outcomes. However, if a pregnant patient in long-term remission wishes to discontinue anti-TNF prior to the third trimester, resumption of anti-TNF shortly after delivery is recommended.
- For women with active disease just before or during pregnancy, or with disease that is difficult to control, continuation of anti-TNF or non-TNF biologics throughout pregnancy is recommended. The last dose of anti-TNF in the third trimester should be timed in accordance with the presumed due date to reduce foetal exposure.
- Anti-TNF antibodies are regarded as low-risk during pregnancy. Data for vedolizumab and ustekinumab are limited, but no increased risk of adverse pregnancy outcomes has been identified.
- Pregnant women experiencing a flare should be managed according to current guidelines for non-pregnant patients, including anti-TNF agents, ustekinumab, or vedolizumab.
- For women in remission treated with non-TNF biologic agents (ustekinumab, vedolizumab), an individualised decision on discontinuing treatment should be made, considering the risk of relapse and the limited data on the consequences of foetal exposure.
- For patients who continue biologics during the entire pregnancy, the treatment should be continued uninterrupted in the postpartum phase unless there is a contraindication to their use. For patients who interrupted treatment during pregnancy, the treatment should be resumed after delivery as soon as possible. Re-induction or continuation of previous maintenance therapy is dependent on clinical circumstances.

ECCO guidelines do not include information on risankizumab and upadacitinib.

There is limited data on the use of golimumab, ustekinumab or vedolizumab in pregnancy. As for other biologics, administration during pregnancy could affect normal immune responses in the newborn.

The decision to continue treatment in pregnancy needs to be individualised, considering all relevant factors (e.g. 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.

The following table is adapted from the available evidence, but prescribers should be aware that guidance may change over time as the evidence base evolves.

Table 4. Pregnancy compatibility and peri-conception

Drug	**Overview of risk during pregnancy** (26)	**Additional information**
Adalimumab	Low risk	BSG and ECCO advise that there is no need to stop anti-TNF. See text above for detailed guidance.
Golimumab	Low risk	BSG and ECCO advise that there is no need to stop anti-TNF. See text above for detailed guidance.
Infliximab	Low risk	BSG and ECCO advise that there is no need to stop anti-TNF. See text above for detailed guidance.
Filgotinib	Contraindicated	Manufacturers recommend that contraception has to continue for 1 week following treatment cessation*
Ozanimod	Contraindicated	Manufacturers recommend that contraception has to continue for 3 months following treatment cessation
Risankizumab	Not included in ECCO guidelines	Manufacturers advise to continue contraception for 21 weeks following treatment cessation**
Tofacitinib	Contraindicated	Manufacturers recommend that contraception has to continue for 4 weeks following treatment cessation*
Upadacitinib	Not included in ECCO guidelines	Manufacturers recommend that contraception has to continue for 4 weeks following treatment cessation*
Ustekinumab	Low risk, limited data	Manufacturers advise to continue contraception for 15 weeks following treatment cessation**
Vedolizumab	Low risk, limited data	Manufacturers advise to continue contraception for 18 weeks following treatment cessation

* However, as effects of JAK inhibitors may persist after drug elimination, a waiting period of one menstrual cycle before conception is advised.

** No guidance for patients with IBD. British Society for Rheumatology advise to continue treatment in rheumatoid arthritis if disease is severe and there are no alternatives.

Further information to support decision-making is available from:

- Summaries of product characteristics (www.medicines.org.uk)
- UK Teratology Information Service (UKTIS) at http://uktis.org/html/exposures_abc.html or 0344 892 0909 (Monday-Friday, 9am-5pm).

Exposures in pregnancy should be reported to UKTIS by use of their online reporting form (http://www.uktis.org/html/reporting.html) UKTIS are commissioned by Public Health England to perform national surveillance of known and emerging human teratogens across the United Kingdom.

Advice and risk assessment for individual patients may also be available by contacting a local Medicines Information service via your trust pharmacy departments.

20.3. Breastfeeding

In general, anti-TNFs are considered compatible with breastfeeding. However, there is limited information on the excretion of biologics in breast milk and subsequent impact on the infant.

ECCO guidelines state that drugs that are considered low-risk during pregnancy are also considered low-risk during breastfeeding and thus can be continued. (26)

Since immunoglobulins are excreted into human breast milk, a risk to the breastfeeding child cannot always be excluded. A decision on whether to breastfeed and continue or discontinue therapy should be made considering the benefit of breastfeeding to the child and the benefit of woman.

Manufacturers of adalimumab advise that this biologic can be used during breastfeeding. (3) For other biologics and JAK inhibitors, manufacturers' recommendations on use in lactation are available from the individual summaries of product characteristics (available from www.medicines.org.uk).

Further information to support decision-making may be available from:

- ECCO Guidelines on Sexuality, Fertility, Pregnancy, and Lactation
- Specialist Pharmacy Service (SPS) website at www.sps.nhs.uk
- Summaries of product characteristics (www.medicines.org.uk)
- Local medicines information service via hospital pharmacy departments.

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

Immunisation schedules in infants after in utero exposure to biologics depends on vaccine type.

The live vaccinations currently included in the childhood vaccination schedule for infants aged <1 year are: (27)

- BCG for tuberculosis – variation across the country depending on incidence of TB. Some areas of GM are considered to have high incidence. Isolated cases of neonates who died from disseminated BCG vaccination or TB infection after exposure to an anti-TNF medicine in utero were reported to MHRA. They were probably not known to be immunosuppressed at the time of vaccination. (28) The BCG vaccine may easily be deferred to be given later in life. (29)
- Rotavirus - all infants. Rotavirus is the most common cause of gastroenteritis in infants in the UK. The rotavirus course of vaccination must be completed by 24 weeks of age due to risk of intussusception. (30) Although there is limited evidence of safety and efficacy in infants with immunosuppression, vaccination of infant exposed in utero may be considered following careful consideration of the risks and benefits and following specialist consultation.

The BSG suggest that for infants exposed in utero to biological therapies: (6)

- BCG vaccination (if indicated) should be withheld until at least 6 months after birth*
- rotavirus vaccine should not be given
- non-live vaccinations may be given according to standard vaccination schedules.

*NB: ECCO guidance recommend withholding vaccination with live attenuated vaccines within the first year of life of the infant. (26) Ultimately, the decision on administration and timing of these vaccinations is with the Obstetrics and Gynaecology and Paediatric departments.

If breastfeeding whilst taking an anti-TNF, childhood vaccinations including the live vaccines rotavirus and BCG may be given following the usual national schedules. 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. (31) For advice on other live vaccinations following exposure to biologics in breastmilk, healthcare professionals should contact the relevant specialist for advice.

21. Vaccinations

21.1. Routine vaccinations

Where possible, vaccination requirements should be reviewed and brought up to date prior to initiation of biologic therapy, with reference to Department of Health Guidance. During biologic therapy, patients should receive (inactivated) influenza vaccine annually and pneumococcal vaccine once only. For vaccination of infants see section 20.4.

21.2. Live vaccines

The administration of live vaccines is contraindicated in patients on biologic agents and cautioned in patients on JAK inhibitors. In the case of ozanimod, the use of live attenuated vaccines should be avoided during and for 3 months after treatment with ozanimod. It is safe to administer a live vaccine 4 weeks prior to commencing treatment with a biologic, a JAK inhibitor or ozanimod, when necessary. There is no contraindication for the administration of live vaccines to relatives or friends of patients on biologic or immunosuppressant drugs.

When a live vaccine is required by a patient on a high cost drug, stopping treatment (following careful assessment of the risks and benefits) may enable a necessary vaccination to be administered. The decision to vaccinate should be guided by the drug half-life (see table 3 in section 19). For further relevant summaries of products characteristics, www.medicines.org.uk

- the Green Book, https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book
- Specialist advice

The table below shows all live vaccines available in the UK.

Table 5. Live vaccines available in the UK

Live vaccine	Brand name
BCG	Bacillus Calmette-Guerin Vaccine
Influenza (nasal)	Fluenz Tetra®
Measles, mumps and rubella combined vaccine (MMR)	MMRvaxPRO®, Priorix®
Rotavirus (Live oral vaccine)	Rotarix®
Typhoid (Live oral vaccine)	Vivotif®
Varicella-Zoster vaccine	Varilrix®, Varivax®, Zostavax®
Yellow Fever	Stamaril®

21.3. Non-live vaccines

Non-live vaccines are deemed safe to administer to people on immunosuppressant and on biologic therapies, though they may elicit a lower response than in immunocompetent individuals.

Non-live vaccines should be given 2-4 weeks before starting immunosuppressant therapy, as response after starting treatment can be poor.

For information on specific vaccines including coronavirus vaccine please refer to the appropriate summary of product characteristics (www.medicines.org.uk) or the Green Book: Immunisation against infections disease.

For information on COVID-19 vaccines please refer to the Green Book: Immunisation against infectious disease Chapter 14a.

Shingrix® a non-live vaccine for varicella zoster virus (VZV) is now available in the UK. From 2021, individuals who are eligible for shingles vaccine (adults aged 70-79 years), but who are contra-indicated to the receipt of the live vaccine should be offered Shingrix® instead. Adults should receive two doses of Shingrix® a minimum of 2 months apart. For more information please refer to the Green Book: Immunisation against infectious disease Chapter 28a.

22. Checklist for patient screening on initiation of high cost drugs

Screening investigations requested in clinic		Y/N	Initial	Results/Details
FBC/U&E/LFT/ESR/CRP				
HIV, HBV *(surface antigen, core antibody)**, **HCV** *(antibody test) If positive result please refer to Hepatology/GUM* * 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				
Varicella Zoster IgG (If negative inform GP and patient)				
TB screening *(g-IFN testing)* *If positive refer to respiratory*				
Chest X-Ray *(within the last 6 months)* *(± pulmonary function tests/HRCT thorax)* **CXR checked by/date**				
TPMT (Before commencing azathioprine therapy)				
Consider: Faecal calprotectin level				
Consider: Ferritin, vitamin B12, folate levels				
Additional monitoring for JAK inhibitors	**Fasting lipids** (if abnormal treat according to local guidelines) Rule out pregnancy			
Additional monitoring for ozanimod	**ECG (check for pre-existing conditions). Blood pressure.** **Rule out pregnancy** **Ophthalmological evaluation of patients with diabetes mellitus, uveitis or a history of retinal disease.**			
Screening questions asked in clinic		**Y/N**	**Initial**	**Details**
Previous TB/TB contact (*details*)				
Travel abroad since last review *(i.e., TB/Viral hepatitis high risk countries)* *Which country/Dates*				
History of heart failure (NYHA class III or IV) *(details)*				
History of recurrent infection *(details)*				
History of interstitial lung disease *(details such as extent of ILD)*				
History of cancer/malignancy *(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 allergy/infusion reaction to any agent *(To what/type of reaction)*				
History of cardiovascular risk factors				
History of thrombotic event (e.g. DVT/PE)				
Any live vaccinations in the last 4 weeks				
History of demyelinating disease (details)				
History of diverticular disease **(details)**				
Concurrent immune disease (e.g., uveitis, ankylosing spondylitis, psoriatic arthritis, psoriasis)				
Education and funding				
Blueteq form completed/request for funding				
Pregnancy/breastfeeding advice given				
Vaccination advice given				
Patient counselled and educated				
Patient consent to be approached for research				

23. Specific monitoring considerations

See screening questionnaire (section 22) for full details of baseline monitoring that should be performed in all patients considered for high cost drugs.

Ongoing monitoring in line with BSG guidance is recommended for all patients, e.g., FBC, creatinine/calculated GFR, ALT/AST and albumin every 3-6 months. (15)

Additional monitoring is recommended for some biologics, JAK inhibitors, and ozanimod as described below. As per MHRA alert, patients on JAK inhibitors should be advised to seek medical advice in signs of cardiovascular medical emergency, and to examine skin periodically and report any new skin growth or changes to moles for potential investigation.

23.1. Ozanimod

FBC (monitoring of absolute lymphocyte count [ALC], absolute neutrophil count [ANC], and haemoglobin) (3)		
Recommended monitoring	• Check FBC at baseline, 4-8 weeks after initiating treatment, and 3-monthly thereafter	
Recommended actions	**ALC** (laboratory value: 10^9 cells/L)	
	ALC > 0.5	Continue treatment
	ALC <0.5	Interrupt treatment. Restart once ALC >0.5.
	ANC (laboratory value: 10^9 cells/L)	
	ANC >1.0	Continue treatment
	ANC <1.0	Interrupt treatment. Restart once ANC >1.0.
Hepatic transaminases		
Recommended monitoring	• Check hepatic transaminases at baseline and thereafter according to routine management (at least monitored every 3 months whilst on treatment)	
Recommended actions	• Temporarily interrupt treatment if drug-induced liver injury is suspected • Interrupt treatment if significant liver injury occurs; liver transaminases above 5 times the upper limit of normal	
Pre-existing cardiac conditions		
Recommended monitoring	• Bradycardia for 6 hours after the first dose	
Recommended actions	• ECG should be obtained before and after 6 hours- consult product literature for further information.	
Eye examination in patients with diabetes or history of uveitis or retinal disease		
Recommended monitoring	• Check before initiation and periodically during treatment NB this does not require a referral to ophthalmology. Check date of last eye scan and reinforce importance of regular attendance for eye checks	
Recommended actions	• Interrupt treatment if macular oedema occurs.	
Blood pressure		
Recommended monitoring	• Regular monitoring during treatment in outpatient clinics (e.g. during scheduled visits for blood tests)	

23.2. Tofacitinib

Monitoring of tofacitinib differs from that of other JAK inhibitors and therefore is tabulated separately.

MHRA: Janus kinase (JAK) inhibitors: new measures to reduce risks of major cardiovascular events, malignancy, venous thromboembolism, serious infections, and increased mortality (2023). It is advised to avoid prescribing JAK inhibitors unless there are no suitable alternatives in patients with the following risk factors: age 65 or older, current, or past long-time smoking and other factors for cardiovascular disease or malignancy.

Dose adjustments are required in hepatic and renal impairment. See below and SPC for further information.

FBC (monitoring of absolute lymphocyte count [ALC], absolute neutrophil count [ANC], and haemoglobin) (3)		
Recommended monitoring	• Check FBC at baseline, 4-8 weeks after initiating treatment, and 3-monthly thereafter	
Recommended actions	**ALC** (laboratory value: cells x 10^9/L)	
	Initiation is not recommended in patients with ALC <0.75	
	ALC >0.75	Maintain dose
	ALC 0.5-0.75	• If ≥2 sequential values in this range, ○ tofacitinib 5 mg BD or 11 mg OD: interrupt dosing • When ALC >0.75, treatment should be resumed as clinically appropriate.
	ALC <0.5	Confirm with repeat testing within 7 days. If confirmed, discontinue
	ANC (laboratory value: cells x 10^9/L)	
	Initiation is not recommended in patients with ANC <1	
	ANC >1	Maintain treatment
	ANC 0.5-1.0	• If ≥2 sequential values in this range, ○ tofacitinib 5 mg BD or 11 mg OD: interrupt dosing • When ANC >1, treatment should be resumed as clinically appropriate.
	ANC <0.5	Confirm with repeat testing within 7 days. If confirmed, discontinue
	Haemoglobin (laboratory value: g/dL)	
	Initiation is not recommended in patients with haemoglobin <9 g/dL	
	Decrease ≤2, and absolute value ≥9	Maintain dose
	Decrease >2 **or** absolute value <8	Confirm with repeat testing. Interrupt dosing until haemoglobin values have normalised.
Hepatic transaminases (ALT & AST)		
Recommended monitoring	• Check hepatic transaminases at baseline and thereafter according to routine management	
Recommended actions	• Temporarily interrupt treatment if drug-induced liver injury is suspected	
Lipid parameters		
Recommended monitoring	• Lipid parameters should be assessed at baseline and repeated after 8 weeks. Maximum effects on lipid parameters are normally seen within 6 weeks. Treat as per local practice guidelines	
Renal impairment		
Recommended actions	• Creatine clearance <30ml/min dose should be reduced to 5mg once daily	
Age considerations		
Recommended actions	• Only use in patients 65 years of age and older if no suitable treatment alternatives are available. • No dose adjustment is required in patients 65 years of age and older. • There is limited data for use in patients aged 75 years and older.	
Other safety considerations (MACE, VTE, malignancy)		
Recommended actions and monitoring	• Patients should be re-evaluated periodically during tofacitinib treatment to assess for changes in VTE risk. • For patients with known risk factors for VTE, consider testing D-dimer levels after approximately 12 months of treatment. If D-dimer test result is ≥ 2× ULN, confirm that clinical benefits outweigh risks prior to a decision on treatment continuation with tofacitinib. • Promptly evaluate patients with signs and symptoms of VTE and discontinue tofacitinib in patients with suspected VTE, regardless of dose or indication. • Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer.	

23.3. Filgotinib and upadacitinib

Monitoring of tofacitinib differs from that of other JAK inhibitors and is tabulated separately. MHRA: Janus kinase (JAK) inhibitors: new measures to reduce risks of major cardiovascular events, malignancy, venous thromboembolism, serious infections, and increased mortality (2023). It is advised to avoid prescribing JAK inhibitors unless there are no suitable alternatives in patients with the following risk factors: age 65 or older, current, or past long-time smoking and other factors for cardiovascular disease or malignancy.

FBC (monitoring of absolute lymphocyte count [ALC], absolute neutrophil count [ANC], and haemoglobin) (3)		
Recommended monitoring	• Check FBC at baseline and then no later than 12 weeks after initiation of treatment	
Recommended actions	**ALC** (laboratory value: 10^9 cells/L)	
	ALC > 0.5	Continue treatment
	ALC <0.5	Interrupt treatment. Restart once ALC >0.5.
	ANC (laboratory value: 10^9 cells/L)	
	ANC >1.0	Continue treatment
	ANC <1.0	Interrupt treatment. Restart once ANC >1.0.
	Haemoglobin (laboratory value: g/dL)	
	Hb >8	Continue treatment
	HB <8	Interrupt treatment. Restart once Hb >8
Hepatic transaminases		
Recommended monitoring	• Check hepatic transaminases at baseline and thereafter according to routine management Note: In the filgotinib SmPC there is no requirement for monitoring of hepatic transaminases.	
Recommended actions	• Temporarily interrupt treatment if drug-induced liver injury is suspected	
Lipid parameters		
Recommended monitoring	• Lipid parameters should be assessed at baseline and repeated after 12 weeks.	
Recommended actions	• Treat any lipid abnormalities in line with local practice.	
Renal impairment		
Recommended actions **Filgotinib**	• A dose of 100 mg of filgotinib once daily is recommended for patients with moderate or severe renal impairment (CrCl 15 to < 60 mL/min). Filgotinib has not been studied in patients with end stage renal disease (CrCl < 15 mL/min) and is therefore not recommended for use in these patients.	
Recommended actions **Upadacitinib**	• No dose adjustment is required in patients with mild or moderate renal impairment. There are limited data on the use of upadacitinib in severe renal impairment and it should be used with caution. In patients with severe renal impairment (eGFR 15 to <30 ml/min/1.73m^2), upadacitinib should be used in caution at once daily dose of 30mg for induction and 15mg for maintenance.	
Age considerations		
Recommended actions **Filgotinib**	• Only use in patients aged 65 years and older if no suitable alternative. The recommended dose is 100 mg once daily and may be escalated to 200 mg once daily in case of insufficient disease control. For long term treatment, the lowest effective dose should be used.	
Recommended actions **Upadacitinib**	• Doses higher than 15 mg once daily for maintenance therapy are not recommended in patients 65 years of age and older. • The safety and efficacy of upadacitinib in patients 75 years of age and older have not yet been established.	
Other safety considerations (MACE, VTE, malignancy)		
Recommended monitoring **Filgotinib** **Upadacitinib**	• Patients should be re-evaluated periodically to assess for changes in VTE risk. • Promptly evaluate patients with signs and symptoms of VTE and discontinue JAK inhibitor in patients with suspected VTE, regardless of dose or indication. • Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.	
Recommended actions **Filgotinib**	• In adults at increased risk of VTE, MACE and malignancy, and those aged 65 and older, the recommended dose is 100 mg once daily and may be escalated to 200 mg once daily in case of insufficient disease control. For long term treatment, the lowest effective dose should be used. *… continued overleaf (for upadacitinib)*	

Recommended actions **Upadacitinib**	• Induction: no dose adjustment. • Maintenance: 15mg for patients at higher risk of VTE, MACE and malignancy; 30 mg once daily may be appropriate for some patients, such as those with high disease burden or requiring 16 week induction treatment who are not at higher risk of VTE, MACE and malignancy or who do not show adequate therapeutic benefit to 15 mg once daily. The lowest effective dose to maintain response should be used.

24. 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:
Harvey R.F. and Bradshaw J.M. A simple index of Crohn's-Disease activity. Lancet. 1980. 1(8167):514. doi: 10.1016/s0140-6736(80)92767-1.

Peyrin-Biroulet L, Panés J, Sandborn WJ, et al. Defining Disease Severity in Inflammatory Bowel Diseases: Current and Future Directions. Clinical Gastroenterology and Hepatology 2016;14:348–354. doi:10.1016/j.cgh.2015.06.001

25. <u>Ulcerative colitis severity scoring and clinical monitoring/ MAYO score</u>

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. doi:10.1056/NEJM198712243172603

Lewis JD, Chuai S, Nissel L, et al. Use of the Noninvasive Components of the Mayo Score to Assess Clinical Response in Ulcerative Colitis. Inflammatory Bowel Disease 2008;14:1660-1666. doi:10.1002/ibd.20520

Peyrin-Biroulet L, Panés J, Sandborn WJ, et al. Defining Disease Severity in Inflammatory Bowel Diseases: Current and Future Directions. Clinical Gastroenterology and Hepatology 2016;14:348–354. doi:10.1016/j.cgh.2015.06.001

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