High cost drugs pathway for psoriatic arthritis in adults

December 2022

Version 1.1 DRAFT (updated March 2023)

This supersedes previous Harmonised Biologics Pathway for AS and PsA (v4.2)

Review due in 2 years from publication

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DOCUMENT CONTROL

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January 2022	Authors	Draft prepared and sent out for consultation	0.1
October 2022	Anna Pracz	Consultation comments review. Alignment with other HCD pathways. Evidence update.	0.2
November 2022	Anna Pracz	Final draft for authors review. Inclusion of updated BSR guidance on drugs in pregnancy and lactation.	0.3 – 0.4
December 2022	Anna Pracz	Submission to CRG and inclusion of comments.	0.5-0.6
March 2023	Anna Pracz	Correction of factual inaccuracies	1.1

Approvals

This document must be approved by the following before distribution:

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Distribution

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

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High cost drugs pathway for psoriatic arthritis in adults

1. Background

This pathway is to be used as a guideline for the use of high cost drugs in treatment of psoriatic arthritis (PsA). It has been written using up to date published research and evidence based medicine. For patients with axial spondyloarthritis, follow the Greater Manchester Medicines Management Group (GMMMG) High cost drugs pathway for axial spondyloarthritis via the GMMMG website.

Currently the pathway includes following classes of high cost disease-modifying anti-rheumatic drugs (DMARDs):

- biologic DMARDs (biologic agents, biologicals)
  - tumour necrosis factor (TNF) alpha inhibitors (anti-TNFs): adalimumab, certolizumab, etanercept, golimumab, infliximab
  - interleukin-17 (IL-17) inhibitors: secukinumab, ixekizumab
  - interleukin-12/23 (IL-12/23) inhibitors: ustekinumab, guselkumab
  - interleukin-23 p19 (IL-23) inhibitor: risankizumab

- targeted synthetic DMARDs (small molecules)
  - phosphodiesterase-4 (PDE4) inhibitor: apremilast
  - Janus kinase inhibitors (JAKi): tofacitinib, upadacitinib

2. NICE guidance

Biological therapies and small molecule high cost drugs are indicated when psoriatic arthritis is active and progressive, i.e. when the patient has peripheral arthritis with three or more tender joint and three or more swollen joints, and the disease has not responded to adequate trial of at least two conventional disease-modifying anti rheumatic drugs (DMARDs), taken either individually or in combination (1) (2) (3). Additional criteria are stipulated by NICE in individual technology appraisal (TA) guidance, e.g. prior anti-TNF failure or intolerance. Notably, patients eligible for risankizumab must have moderate to severe psoriasis and a Psoriasis Area and Severity Index (PASI) score greater than 10 (4). See table 2 in section 12 for more information.

Links to the relevant NICE guidelines and technology appraisals 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 same indication. (5)

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.

NICE NG65 Spondyloarthritis in over 16:diagnosis and management

NICE CG153 Psoriasis: assessment and management

2.1. Biologic DMARDs

- NICE TA199 (2010): Etanercept, infliximab & adalimumab for the treatment of psoriatic arthritis
- NICE TA220 (2011): Golimumab for the treatment of psoriatic arthritis
- NICE TA340 (2017): Ustekinumab for treating active psoriatic arthritis
- NICE TA445 (2017): Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs
- NICE TA537 (2018): Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs
- NICE TA803 (2022): Risankizumab for treating active psoriatic arthritis after inadequate response to DMARDs
- NICE TA815 (2022): Guselkumab for treating active psoriatic arthritis after inadequate response to DMARDs

2.2. Targeted synthetic DMARDs

- NICE TA433 (2017): Apremilast for treating active psoriatic arthritis
- NICE TA543 (2018): Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs
- NICE TA768 (2022): Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs

3. Initiating treatment with a high cost drug

All NICE-approved high cost drugs for treatment of psoriatic arthritis are routinely commissioned if prescribed in accordance with this pathway and used in line with criteria 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.

Patients with psoriatic arthritis may present with other extra-articular manifestation (inflammatory bowel disease, psoriasis or uveitis). (6) Those with concomitant inflammatory disorders may benefit from a drug that is also indicated for this comorbidity and approved under the appropriate GMMMG High Cost Drugs Pathway. See also table 2 in section 12 for drug choice.

There are further numerous factors which may influence the choice of drug at each point in the pathway, including disease presentation with activity in different domains, co-morbidities, dexterity, previous treatment history and adherence, route of administration, frequency, devices available. (6) These factors should be considered in a discussion between the patient and their clinician, including the advantages and disadvantages. The rationale for choice should be documented.

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. See GMMMG (2016): Prescribing of high cost biosimilar biological medicines. Clinicians should also contact pharmacy for advice on the relative cost-effectiveness 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 applicable.

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 ongoing pharmacovigilance of the individual products.

Pharmacovigilance is essential for any new high cost drug medicine (including biosimilars and newer classes of drugs, e.g. JAK inhibitors) and additional monitoring is indicated through the MHRA's Black Triangle Scheme.

Patients should be enrolled on to the relevant registry which serves data collection on the safety and effectiveness of medicines in clinical practice. See section 11 for more on registries.

Treatment should be reviewed initially to assess efficacy as per relevant NICE guidance (12-24 weeks), and thereafter at least every 6 months. (6) (7) For treatment pathway, see flowcharts in section 13. For specific treatment selection criteria see table 2 in section 12 lists available treatments.

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 British Society for Rheumatology (BSR) have published a biosimilar position statement which states:

- When considering switching patients on a biologic originator product to a biosimilar, patients must be provided with sufficient information to make an informed decision, with the support of their rheumatology multidisciplinary team.
- No patients should be switched from one biosimilar to another biosimilar of the same originator product purely based on cost, as there are potential concerns over patient safety and immunogenicity.
- When the specific biologic prescribed is unavailable, the dispensing pharmacist must contact the prescribing clinician to seek advice as to appropriate short-term alternatives. The patient must be always informed about any discussions concerning their medicine.

Furthermore, the GMMMG advised in its statement on biosimilar, regarding changing from originator to a biosimilar (5):

- There is evidence that patients who are in a stable clinical response or remission may be changed over to the biosimilar at the same dose and dose interval. This should be done after discussion and agreement with individual patients.
- Changing a patient on a biologic originator medicine to a biosimilar should be done at the point of prescribing and in discussion with the hospital pharmacy department.
- There should be no automatic substitution of a biologic with a biosimilar at the 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 the same manufacturer, 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 (8).

For some drugs, reduced doses are indicated in the elderly, renal impairment, hepatic impairment and according to blood test results – see section 20 for specific monitoring considerations and summary of product characteristics for adjusted dosing.

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

Patients with psoriatic arthritis may present with other extra-articular (inflammatory bowel disease, psoriasis or uveitis). (6) Those with concomitant inflammatory disorders may benefit from a drug that is also indicated for this comorbidity and approved under the appropriate GMMMG High Cost Drugs Pathway. See also table 2 in section 12 for drug choice.

Table 1. Standard and alternative HCD regimens (8)

Drug	Standard maintenance dose	Alternative regimes
Adalimumab (SC)	40mg every two weeks	Not specified in the marketing authorisation
Apremilast (PO)	30mg twice daily	Not specified in the marketing authorisation
Certolizumab pegol (SC)	200 mg every 2 weeks	400mg every 4 weeks, once clinical response is confirmed
Etanercept (SC)	50mg once weekly	25mg twice weekly
Golimumab (SC)	50 mg monthly	100mg monthly, in patients >100 kg who do not achieve an adequate response on 50 mg monthly after 3-4 doses
Guselkumab (SC)	100mg every 8 weeks	100mg every 4 weeks based on clinical judgement if considered high risk of joint damage
Infliximab (IV)	5mg/kg every 8 weeks	Not specified in the marketing authorisation
Ixekizumab (SC)	80mg every 4 weeks	For patients with concomitant moderate to severe plaque psoriasis, the recommended dosing regimen is the same as for plaque psoriasis: 80mg after 2 weeks, then 80mg every 2 weeks for 5 further doses (at weeks 4, 6, 8, 10 and 12) then maintenance at 80mg every 4 weeks

Drug	Standard maintenance dose	Alternative regimes
Risankizumab (SC)	150mg every 12 weeks	Not specified in the marketing authorisation
Secukinumab (SC)	150mg monthly	300 mg monthly, based on clinical response or presence of concomitant psoriasis and inadequate anti-TNF response
Tofacitinib (PO)	5mg twice daily or 11mg prolonged-release tablets once daily	Not specified in the marketing authorisation
Upadacitinib (PO)	15mg once daily	Not specified in the marketing authorisation
Ustekinumab (SC)	45mg every 12 weeks	90mg every 12 weeks, in patients >100 kg

IV – intravenous; PO - oral; SC – subcutaneous

In sustained remission, tapering of biologics agents should be considered. (6)

6. Treatment failure with a high cost drug

Although many patients initially respond well to fist-line treatment, they may subsequently lose response. A proportion of patients also do not respond to the chosen treatment at all. For those non-responders, as well as in patients where drug needs to be discontinued as described below, switching therapy is required to achieve and maintain treatment targets. (6) For the purposes of this pathway, this can include failure due to inefficacy:

- Primary failure: the psoriatic arthritis disease activity does not respond adequately to a high cost drug within the timescales defined in the marketing authorisation and NICE technology appraisal (see section 2)
- Secondary failure: the psoriatic arthritis disease activity 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 observed. In effect, changes to therapy may 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 relative or absolute contraindication
- patient becoming pregnant (see section 17.2)

7. Sequential use of high cost drugs

Prior to switching to a subsequent treatment, consideration may 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 predictive of a patient's likely response to alternative agents in an alternative class, or even in the same class. (9)

High cost drugs for psoriatic arthritis currently have several different molecular targets (e.g. TNFα, IL-6, IL-12/23, JAK), 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.

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, 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 high cost drug to another. There are very little published data on this topic. The following should be considered when switching: clinical circumstances, drug levels (where appropriate), half-life of the drug (table 3 in section 16), safety (e.g. bridging with steroids) and practical considerations. The next drug could be started when the previous drug was due next dose or at least after one-half life of current drug has passed (whichever is longer).

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. 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 or equivalent, where commissioned.

Where available and subject to contractual arrangements Blueteq or equivalent 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 (or equivalent) 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).

9. Individual funding requests (IFR)

Individual funding request 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.

10. Free of charge schemes

All free of charge schemes must be approved in accordance with trust guidance and the GMMMG Free of Charge guidance. (10) 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.

11. Research

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

Clinicians are strongly encouraged to participate in long-term safety studies or registries such as OUTPASS or BSR-PsA. In addition, opportunities for local observational research studies may also be considered.

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

12. 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.

Patients with psoriatic arthritis may present with other extra-articular (inflammatory bowel disease, psoriasis or uveitis). (6) Those with concomitant inflammatory disorders may benefit from a drug that is also indicated for this comorbidity and approved under the appropriate GMMMG High Cost Drugs Pathway. See also table 2 below.

Note that all bDMARDs and JAK inhibitors may increase infection risk. 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.

Biological DMARDs and JAK inhibitors should be given in combination with MTX, unless MTX is contraindicated or withdrawn due to adverse events. In specific clinical circumstances, most bDMARDs can be used as monotherapy* (non-methotrexate cDMARD or no cDMARD).

Abbreviations

bDMARD – biological DMARD (adalimumab, etc) cDMARD – conventional DMARD (methotrexate, etc) HCD – high cost drug JAK inhibitors – Janus kinase inhibitors (baricitinib, etc)
MTX – methotrexate PASI – Psoriasis Area Severity Index PDE - phosphodiesterase PsARC – Psoriatic Arthritis Response Criteria
TB – tuberculosis UC – ulcerative colitis VTE/PE – venous thromboembolism /pulmonary embolism

Table 2.Available HCDs – information to support choice

Drug & route of administration	Mode of action	First line?	Initial review[1]	Supplementary information. This list is not exhaustive – refer to SCP for details on individual drugs.	Monotherapy (as per NICE TA and on label)	Offer (*preferably) for patients with (11)		
						dactylitis	enthesitis	nail psoriasis
Adalimumab (SC)	TNF-inhibitor	Yes	12 weeks	Licensed & NICE-approved in psoriasis (TA146), Crohn's (TA187), UC (TA329), hidradenitis suppurativa (TA392), uveitis (TA460)	✓	✓	✓	✓ *
Apremilast (PO)	PDE-4 inhibitor	Yes	12 weeks	NICE-approved in psoriasis (TA419).	✓ or use with any cDMARD	✓	✓	✓
Certolizumab pegol (SC)	TNF-inhibitor	Yes	12 weeks	Consider first line in women who are pregnant or breastfeeding, or who are likely to become pregnant during treatment (8) (12) NICE-approved in psoriasis (TA574). Licensed in US (but not UK) for Crohn's (Cochrane). Some evidence for efficacy in uveitis (13), but no licence.	✓ or use with MTX	✓	✓	✓ *
Etanercept (SC)	TNF-inhibitor	Yes	12 weeks	NICE-approved in psoriasis (TA103), but not in GMMMG psoriasis pathway due to lower efficacy. Consider if anti-TNF is otherwise appropriate, but patient at risk of TB or has potential serious infection risk or previous hospitalisation for infection while on anti-TNFs (7) (14)	✓	✓	✓	✓

[1] As per relevant NICE TA

Drug & route of administration	Mode of action	First line?	Initial review[2]	Supplementary information. This list is not exhaustive – refer to SCP for details on individual drugs.	Monotherapy (as per NICE TA and on label)	Offer (*preferably) for patients with (11)		
						dactylitis	enthesitis	nail psoriasis
Golimumab (SC)	TNF-inhibitor	Yes	12 weeks	NICE-approved in UC (TA329). **NB: not licensed for psoriasis.** Consider for use in patients weighing >100kg (higher dose licensed in this population).	✓ or use with MTX	✓	✓	✓ *
Guselkumab (SC)	IL-23 inhibitor	2nd line*	16 weeks	*only if anti-TNF failed or not suitable NICE-approved in psoriasis (TA521).	✓ or use with MTX	✓	✓	✓ *
Infliximab (IV)	TNF-inhibitor	Yes	12 weeks	NICE-approved in psoriasis (TA134), Crohn's (TA187), UC (TA329). Some evidence for efficacy in uveitis (7) (15), but no UK licence.	✓ or use with MTX	✓	✓	✓ *
Ixekizumab (SC)	IL-17 inhibitor	Yes	16 weeks	NICE-approved in psoriasis (TA442).	✓ or use with MTX	✓	✓	✓ *
Risankizumab (SC)	IL-23 inhibitor	2nd line**	16 weeks	**** must have had anti-TNF and only if comorbid moderate to severe psoriasis and PASI score >10 (as per TA803)** NICE-approved in psoriasis (TA596)	✓ or use with MTX	✓	✓	✓ *
Secukinumab (SC)	IL-17 inhibitor	Yes	16 weeks	NICE-approved in psoriasis (TA350).	✓ or use with MTX	✓	✓	✓ *
Tofacitinib (PO)	JAK inhibitor	Yes	12 weeks	NICE-approved in UC (TA547)	Must use with MTX	✓	✓	✓
Upadacitinib (PO)	JAK inhibitor	2nd line*	12 weeks	*only if anti-TNF failed or not suitable Licensed for UC Can be used as monotherapy or with MTX (on label and within NICE)	✓ or use with MTX	✓	✓	✓
Ustekinumab	IL-12/23 inhibitor	2nd line*	24 weeks	*only if anti-TNF failed or not suitable NICE-approved in psoriasis (TA180), Crohn's disease (TA456). Consider for use in patients weighing >100kg	✓ or use with MTX	✓	✓	✓ *

[2] As per relevant NICE TA

13. GM High cost drugs pathway for psoriatic arthritis

Active psoriatic arthritis despite ≥2 conventional DMARDs

At all stages when treating with HCD
- Consider entry to a trial or registry (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 19 for high cost drug screening questions for pre-admission.

First line (HCD-naive): choose based on clinical factors and best value
For more details see section 12 and purple box to the right

Treat to target (11) **Review at 12-16 weeks**, as per NICE guidance (see sections 2 and 12)

Adequate response
- Improvement in at least two PsARC criteria (one of which must be joint tenderness or swelling)
- No worsening in any of the four PsARC criteria
- Treatment tolerated

Continue treatment

Review every 6 months

When treatment targets met:
Taper and stop cDMARDs:
- Unless required to continue by license
- To maximise psoriasis response (MTX)
- Required to improve persistence (anti-TNF)
- Comorbid conditions (IBD/uveitis)

In sustained remission: consider tapering (11)

Inadequate response

Consider potential factors that could be addressed including: confirming correct diagnosis, adherence, pain due to other causes, drug levels and immunogenicity. Discuss with dermatology if response in PASI but not PSARC.

Secondary failure
- Loss of response (i.e. loss of PsARC improvement, or PsARC worsening)
- Emerging adverse drug reactions or novel contraindications

Primary failure

Criteria for adequate response not met within timescales defined by NICE

Optimise dose prior to switching, if possible

Review patient factors & adherence. Discuss with dermatology if response in PASI but not PSARC. Review cDMARD; consider MTX. If on anti-TNF and measurement of trough drug levels and anti-drug antibodies available, consider performing testing, ideally within 24 hours of next dose. (24)

Choose alternative high cost drug:
- Consider a different mode of action if primary inefficacy to previous HCD
- Consider domains of disease, previous medication use, pain due to other causes, drug levels, immunogenicity
- See purple box and table 2 in section 12 for choice

Therapeutic drug monitoring (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

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

Drug levels low /undetectable and ADAb +ve
Potential loss of response.
- Add in cDMARD
- Switch to another anti-TNF*
- Swap to non-anti-TNF or JAK inhibitor

Drug level within or above range/ ADAb +/-ve and clinical loss of response
Likely non-TNF driven disease.
Switch to:
- non-anti-TNF
- JAK inhibitor

*Consider etanercept if not already used as considered less immunogenic (24) or appropriate alternative (if ADAb levels allow)

Anti-TNF drug level & antibodies undetectable -assess adherence, increase drug dose and frequency if appropriate – see section 5. Consider BMI: Is dose weight-adjusted? If adjustments do not result in adequate response, consider switching to alternative bDMARD or JAK inhibitor. See section 12 for choice.

- **For arthritis consider:** Anti-TNF, IL17 and JAKi (upadacitinib) ahead of IL23, IL22/23 ahead of PDE4
- **For psoriasis consider:** Monoclonal anti-TNF (adalimumab, certolizumab, infliximab), IL17, IL23, IL12/23
- **For axial disease consider:** Anti-TNF, IL17, JAKi (upadacitinib)
- **If moderate/severe or recurrent uveitis – consider:** Adalimumab, infliximab, certolizumab
- **If Crohn's disease consider:** Adalimumab, infliximab, certolizumab, ustekinumab
- **If ulcerative colitis consider:** Adalimumab, infliximab, golimumab, JAKi (tofacitinib)

14. Contraindications, special warnings and precautions

14.1 Cautions and contraindications

Cautions, contraindications, and special warnings regarding use of systemic agents for psoriatic arthritis are detailed in the individual summaries of products characteristics (SPCs), which are available from www.medicines.org.uk. Prescribers should consult the relevant SPC to inform clinical decision-making for individual patients, which is beyond the scope of this guideline. For further guidance, see The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis.

14.2 Additional safety considerations

The MHRA has published Drug Safety Updates relating to several of the drugs included in this pathway. Visit www.gov.uk/drug-safety-update for up to date information on safety issues.

- Tofacitinib (Xeljanz▼): new measures to minimise risk of major adverse cardiovascular events and malignancies, 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; 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.
- Apremilast (Otezla▼): risk of suicidal thoughts and behaviour; 2017. Stop treatment if patients have new psychiatric symptoms or if existing symptoms worsen.
- Live attenuated vaccines: avoid use in those who are clinically immunosuppressed; 2016
- Ustekinumab (Stelara): risk of exfoliative dermatitis; 2015. If you suspect exfoliative dermatitis caused by an adverse reaction to ustekinumab, stop treatment.
- Tumour necrosis factor alpha inhibitors; 2014. Risk of tuberculosis - screen all patients before starting treatment and monitor them closely.

In November 2022, the European Medicines Agency published results of review of the safety of JAK inhibitors. The recommendations include restricting use of these drugs in some patient groups to reduce the risk of serious side effects with JAK inhibitors. The MHRA has said it will look at safety measures around use of JAK inhibitors. (16) Until then clinical judgement is necessary to determine best drug choice for individual patient.

14.3 Malignancy

The use of rheumatology 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 advise on treatment might be sought.

15. Pre-high cost drug screening

Please refer to the checklist provided at the end of the document (section 19), which can be adapted locally if necessary.

15.1. Tuberculosis (TB)

Interferon gamma (gIFN) testing is recommended prior to commencing biologic, JAK inhibitor or other small molecule high cost drug 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 (17) and refer for a respiratory opinion if deemed necessary: See NICE guideline NG33, Tuberculosis (Sept 2019) for further information.

With anti-TNF therapy, risk of TB reactivation appears lowest in etanercept compared to monoclonal antibodies (infliximab and adalimumab). (7) There also appears to be a signal of concern from clinical trials with newer monoclonal antibodies such as certolizumab and golimumab, however data from observational studies is currently lacking. (7)

15.2. Hepatitis B & C

Screening for hepatitis B and C is recommended for all patients starting a biologic and JAK inhibitors or other small molecule high cost drug. BSR guidance recommends that screening should include: (7)

- 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 biological DMARD may be appropriate but should follow a risk/benefit decision made with a hepatologist, infectious disease or another relevant specialist.

15.3. Human immunodeficiency virus (HIV)

Screening for HIV is recommended for all patients starting a rheumatology high cost drug. NICE Quality Standard QS157 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. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis recommends risk factors for HIV infection should be documented prior to commencing a high cost drug and, if present, an HIV test should be performed. If considering the use of a high cost drug in HIV positive patients, this should be discussed with an HIV specialist.

16. Surgery and perioperative risk

Potential benefit of reduced risk of post-operative infections by stopping treatment should be balanced against risk of flare in disease activity. For most treatments consideration should be given to planning surgery when at least one dosing interval has elapsed for that specific drug. (7)

For higher risk procedures consider stopping 3–5 half-lives (if this is longer than one dosing interval) before surgery. In all cases, rheumatology consultant should be involved.

High cost drugs should be recommenced after surgery when there is evidence of good wound healing (typically around 14 days), all sutures and staples are out, and there is no evidence of infection. For further guidance, see The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis or review trust's perioperative guidelines if applicable.

Table 3. Peri-operative supportive information (8) (7) (18) (19)

Drug	Dosing interval	Period in which surgery should be scheduled (relative to last drug dose administered)	One mean half-life	Five half-lives
Adalimumab	Every 2 weeks	Week 3	14 days	70 days
Apremilast	Twice daily	Can continue if not high risk	9 hours	~2 days
Certolizumab pegol	Every 2 weeks Every 4 weeks	Week 3 Week 5	14 days	70 days
Etanercept	Weekly or twice weekly	Week 2	3 days	15 days
Golimumab	Every 4 weeks	Week 5	14 days	70 days
Guselkumab	Every 8 weeks	Week 9	17 days	85 days
Infliximab IV	Every 4, 6 or 8 weeks	Week 5, 7 or 9	9 days	45 days
Ixekizumab	Every 4 weeks	Week 5	14 days	70 days
Risankizumab	Every 12 weeks	Week 13*	29 days	145 days
Secukinumab	Every 4 weeks	Week 5	30 days	150 days
Tofacitinib	Twice daily	Day 4**	3 hours	15 hours
Tofacitinib MR	Once daily	Day 4**	6 hours	30 hours
Upadacitinib	Once daily	Day 4**	14 hours	3 days
Ustekinumab	Every 12 weeks	Week 13	21 days	105 days

*****No published guidance available, recommendation based on half-life (8) and dosing interval (7).
******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 (8). 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.

17. Fertility, pregnancy and lactation

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 BSR pregnancy and breastfeeding guideline renewed in October 2022 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.

17.1. 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 (see table 4 in section 17.2). **Paternal exposure to high cost drugs included in this pathway is compatible with pregnancy.** (20)

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.

17.2. Pregnancy

Among biologics, anti-TNFs, can be considered during pregnancy. The BSR (20) advise that:

- Women stable on anti-TNF therapy with known placental transfer (adalimumab, infliximab, golimumab) do not need to be switched to an anti-TNF with established minimal placental transfer (certolizumab) before or during pregnancy.
- Certolizumab due to no to minimal rate of transplacental transfer, can be considered for use thorough pregnancy.
- Patients who stop anti-TNF therapy during pregnancy may, if needed, be re-loaded as soon as possible after delivery to manage maternal disease, given infection or other complications of postpartum are excluded, and regardless of breastfeeding status.
- Lower grade, limited evidence is available for IL-17 and IL-12/23 inhibitors and is insufficient to recommend for use in pregnancy, unless there are no alternatives to control severe disease.
- JAK inhibitors are contraindicated and should be stopped at least two weeks pre conception and should not be used during breastfeeding.

No studies for apremilast and upadacitinib were identified in the guidance review; guselkumab and risankizumab were not included in evidence searches.

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 contains advice from BSR and also lists manufacturers' recommendations on time to continue contraception after treatment cessation and compatibility with pregnancy trimesters.

For stopping biologics in pregnancy to enable infant vaccinations per UK schedule see section 17.4.

Table 4. Peri-conception and pregnancy compatibility

Drug	**Time to continue contraception after treatment cessation [SPCs]** (8)	**Compatibility with trimesters [BSR 2022]** (20)		
		Peri- conception	**First**	**Second/ Third**
Adalimumab	5 months	Yes	Yes	Yes
Apremilast	No advice	No studies identified in BSR guidance		
Certolizumab	5 months	Yes	Yes	Yes
Etanercept	3 weeks	Yes	Yes	Yes
Golimumab	6 months	Yes	Yes	Yes
Guselkumab	12 weeks	Not included in BSR guidance.		
Infliximab	6 months	Yes	Yes	Yes
Ixekizumab	10 weeks	Consider stopping at conception**	Severe disease if no alternatives**	Severe disease if no alternatives
Risankizumab	21 weeks	Not included in BSR guidance		
Secukinumab	20 weeks	Consider stopping at conception**	Severe disease if no alternatives**	Severe disease if no alternatives
Tofacitinib*	4 weeks	Stop ≥2 weeks pre-conception	No	No
Upadacitinib*	4 weeks	Stop ≥2 weeks pre-conception	No	No
Ustekinumab	15 weeks	Consider stopping at conception**	Severe disease if no alternatives**	Severe disease if no alternatives

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

** May be considered to manage severe maternal disease if no other pregnancy-compatible drugs are suitable.

Further information to support decision-making is available from:

- BSR guidance on prescribing of drugs in pregnancy and lactation
- Summaries of product characteristics (www.medicines.org.uk)
- UK Teratology Information Service (UKTIS) at https://uktis.org or 0344 892 0909 (Monday-Friday, 9am-5pm).

Exposures in pregnancy should be reported to UKTIS by use of their online reporting form (https://uktis.org/surveillance/reporting-an-exposure-in-pregnancy/). UKTIS are commissioned by the UK Health Security Agency (formerly Public Health England) to perform national surveillance of known and emerging human teratogens across the UK.

Advice and risk assessment for individual patients may also be available by contacting a local medicines information service via hospital pharmacy departments.

17.3. Breastfeeding

Biologics in general, and in particular anti-TNFs, are considered compatible with breastfeeding. The BSR (20) advise that:

- Anti-TNFs are compatible with breastfeeding.
- Based on limited evidence, non-anti-TNF biologics are compatible with breastfeeding (but note no data on guselkumab and risankizumab to date).
- JAK inhibitors should be avoided in breastfeeding.
- No data for apremilast to date.

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.

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

- BSR guidance on prescribing of drugs in 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.

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

Immunisation schedules in infants after in-utero exposure to biologics will depend on timing of exposure, bioavailability and persistence of the drug, mechanism of action of the drug, and live vaccine. (20) The BSR recommend that:

- Women considered to have low risk of disease flare on withdrawal of anti-TNF in pregnancy could stop infliximab at 20 weeks, adalimumab and golimumab at 28 weeks and etanercept at 32 weeks so that a full-term infant may receive the normal UK vaccination schedule, including rotavirus vaccine at 8 weeks.
- Adalimumab, etanercept, infliximab or golimumab may be continued throughout pregnancy, to maintain disease control. In such case, immunisation with live vaccines should be avoided until infants are 6 months of age.
- Exposure to certolizumab in utero does not require any changes to vaccination schedule.

Table 5. Pregnancy exposure and impact on infant live vaccines schedule (20)

Drug	Pregnancy exposure and impact on infant live vaccines schedule
Adalimumab	If stopped by 28 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Apremilast	No studies found in last BSR guidance update.
Certolizumab	No adjustment to vaccination including live vaccines needed.
Etanercept	If stopped by 32 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Golimumab	If stopped by 28 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Guselkumab	Not included in BSR guidance.
Infliximab	If stopped by 20 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Ixekizumab	If used to treat severe maternal disease in the third trimester, avoid all live vaccines in the infant vaccination schedule until 6 months of age.
Risankizumab	Not included in BSR guidance.
Secukinumab	If used to treat severe maternal disease in the third trimester, avoid all live vaccines in the infant vaccination schedule until 6 months of age.
Ustekinumab	If used to treat severe maternal disease in the third trimester, avoid all live vaccines in the infant vaccination schedule until 6 months of age.
JAK inhibitors	Not applicable. Contraindicated in pregnancy.

The live vaccinations currently included in the childhood vaccination schedule for infants aged <1 year are: (21)

- 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. (22) The BCG vaccine may easily be deferred to be given later in life. (20)
- 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. (23) 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.

For advice on other live vaccinations following exposure to biologics in breastmilk, healthcare professionals should contact the relevant specialist for advice.

If there is any doubt as to whether an infant due to receive a live attenuated vaccine may be immunosuppressed due to the mother's therapy, including exposure through breast-feeding, specialist advice should be sought. (23)

Current vaccination strategies with non-live vaccines for infants who have been exposed to biologic medicines *in utero* do not differ from those for unexposed infants.

18. Vaccinations

Where possible, vaccination requirements should be reviewed and brought up to date prior to initiation of high cost drug therapy, with reference to Department of Health Guidance. (23) (21) During high cost drug therapy, patients should receive (inactivated) influenza vaccine annually and pneumococcal vaccine once only. For vaccination of infants see section 17.4.

18.1. Live vaccines

The administration of live vaccines is contraindicated in patients on biologic agents and cautioned in patients on JAK inhibitors. It is safe to administer a live vaccine 4 weeks prior to commencing biologic or tofacitinib therapy, 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 16). 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 (23)
- Specialist advice

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

Table 6. Live vaccines available in the UK

Live vaccine	Brand name
Tuberculosis - BCG	Bacillus Calmette-Guerin Vaccine
Influenza (nasal)	Brand can change yearly in the UK
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®

18.2. Non-live vaccines

Non-live vaccines are deemed safe to administer to people on immunosuppressant and on high-cost 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 please refer to the appropriate Summary of Product Characteristics (www.medicines.org.uk) or the Green Book: Immunisation against infectious disease. (23)

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 (23)

19. Checklist for patient screening on selection for high cost drugs

Screening investigations requested in clinic				
		Y/N	**Initial**	**Results/Details**
FBC/U&E/LFT/ESR/CRP				
ANA *(If positive also order ENA/dsDNA/C3/C4)*				
HIV, HBV *(surface antigen, core antibody)**, **HCV** *(antibody test) If positive result please refer to hepatology/GUM/ID as relevant* * 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**				
Additional monitoring: **JAK inhibitors**	**Fasting lipids** (if abnormal treat according to local guidelines)			
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, IBD, psoriasis)				
Education				
Pregnancy/breastfeeding advice given				
Vaccination advice given				
Patient counselled and educated				
Patient consent to be approached for research				

20. Specific monitoring considerations

See screening questionnaire (section 19) for full details of baseline monitoring that should be performed in all patients considered for high cost drugs.

Ongoing monitoring in line with BSR guidance is recommended for all patients, e.g. FBC, creatinine/calculated GFR, ALT/AST and albumin every 3-6 months. (7)

Additional monitoring is recommended for some biologics and for the JAK inhibitors, as described below.

20.1 Tofacitinib

Dose adjustments are required in hepatic and renal impairment, See SPCs for further information.

MHRA alert: Tofacitinib Drugs Safety Update, 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 (such as diabetes or coronary artery disease) or malignancy risk factors unless there are no suitable treatment alternatives.

FBC (monitoring of absolute lymphocyte count [ALC], absolute neutrophil count [ANC], and haemoglobin) (8)		
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	

20.2 Upadacitinib

FBC (monitoring of absolute lymphocyte count [ALC], absolute neutrophil count [ANC], and haemoglobin) (8)		
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.	
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 **Upadacitinib**	• No dose adjustment is required in patients with mild or moderate renal impairment. There are limited data on the use of upadacitinib in subjects with severe renal impairment. Upadacitinib 15 mg once daily should be used with caution in patients with severe renal impairment.	

20.3 Guselkumab

Hepatic transaminases	
Recommended actions (8)	• When prescribing four weekly dose, check hepatic transaminases at baseline and thereafter according to routine patient management. If increases in alanine aminotransferase [ALT] or aspartate aminotransferase [AST] are observed and drug-induced liver injury is suspected, temporarily interrupt treatment until this diagnosis is excluded

20.4 Apremilast

Dose reduction required in renal impairment, see SPC for further information

Renal impairment	
Recommended actions	• A dose of 30mg once daily is recommended in patients with severe renal impairment (CrCl < 30mLmin). During dose titration, it is recommended using the AM scheduled dose only (the PM dose should be skipped)
Mental health	
Recommended actions	• Suicidal thoughts and behaviour, including completed suicide, have been reported in patients with or without a history of depression • Carefully assess the benefits and risks of starting or continuing treatment in patients with a history of psychiatric symptoms, or in those who are taking other medicines likely to cause psychiatric symptoms • Patients should be instructed to report any changes in behaviour and treatment should be stopped if patients experience new psychiatric symptoms or if existing symptoms get worse.

21. References

1. NG 65. Spondyloarthritis in over 16s: diagnosis and management. NICE. 2017.

2. TA543 Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs. NICE. October 2018.

3. TA768 Upadacitinib for treating active psoriatic arthritis after inadequate response to DMARDs. NICE. February 2022.

4. TA803 Risankizumab for treating active psoriatic arthritis after inadequate response to DMARDs. NICE. July 2022.

5. Prescribing of high cost biosimilar biological medicines. GMMMG. s.l. : Accessed via https://gmmmg.nhs.uk/guidance/high-cost-drugs/, 2016.

6. The 2022 BSR guideline for the treatment of psoriatic arthritis with biologics and targeted syntetic DMARDs. Tucket L., et al.,. s.l. : Rheumatology, 2022. https://doi.org/10.1093/rheumatology/keac295.

7. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis. Holroyd, C R, Seth, R and Mukhari, M. 2, 2019, Rheumatology, Vol. 58, pp. e3-e42.

8. Summaries of product characteristics, accessed via electronic Medicines Compendium at https://www.medicines.org.uk/emc/.

9. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Smolen, JS, et al. 2020, Ann Rheum Dis, Vol. 0, pp. 1-15.

10. Free of charge (FOC) medicines schemes. Committee, Regional Medicines Optimisation. Accessed via https://gmmmg.nhs.uk/guidance/high-cost-drugs/, 2018.

11. The 2022 British Society for Rheumatology guideline for the treatment of psoriatic arthritis with biologic and targeted synthetic DMARDs. Tucker, L. et al. ,. 9, s.l. : Rheumatology, 2022, Vol. 61. Pages e255–e266.

12. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. al, Russel et. s.l. : Rheumatology, 2022, Rheumatology, Vol. 00, pp. 1693-7. https://doi.org/10.1093/rheumatology/keac551.

13. Reduction of anterior uveitis flares in patients with axial spondyloarthritis on certolizumab pegol treatment: final 2-year results from the multicenter phase IV C-VIEW study. van der Horst-Bruinsma IE, et al. 29;13:1759720X211003803., s.l. : Ther Adv Musculoskelet Dis., 2021. https://pubmed.ncbi.nlm.nih.gov/33854572/.

14. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Singh, JA, et al. 1, 2016, Vol. 68, pp. 1-25.

15. Guidance on noncorticosteroid systemic immunomodulatory therapy in noninfectious Uveitis: fundamentals Of Care for UveitiS (FOCUS) initiative. Dick AD, et al. s.l. : Ophthalmology, 2018, Vols. 125:757–773.

16. UK medicine regulator considering safety measures for JAK inhibitors following new guidance. Robinson, J. s.l. : Pharmaceutical Journal, Nov 2022 . https://pharmaceutical-journal.com/article/news/uk-medicine-regulator-considering-safety-measures-for-jak-inhibitors-following-new-guidance.

17. You can't always get what you want, but if you try sometimes (with two tests - TST and IGRA - for tuberculosis) you get what you need. Winthrop, KL; Weinblatt, ME; Daley, CL. 11, 2012, Ann Rheum Dis, Vol. 71, pp. 1757-60.

18. Guideline for the Perioperative Management of Antirheumatic Medication in Patients. Goodman, S.M., et al. American College of Rheumatology/American Association of Hip and Knee Surgeons. s.l. : Arthritis Care Res, 2022. https://doi.org/10.1002/acr.24893.

19. BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. . al, Ledingham J et. s.l. : Rheumatology (Oxford)., 2017 Jun 1;, Vols. 56(6):865-868. . doi: 10.1093/rheumatology/kew47.

20. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. Russel et al. s.l. : Rheumatology, 2022, Rheumatology, Vol. 00, pp. 1693-7. https://doi.org/10.1093/rheumatology/keac551.

21. The complete routine immunisation schedule from February 2022. UK Health Security Agency. 2022.

22. Drug Safety Update. Live attenuated vaccines: avoid use in those who are clinically immunosuppressed. MHRA. 2016.

23. Immunisation against infectious disease: the green book. UK Health Security Agency. 2022 (last update).

24. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory disease: a real issue, a clinica perspective. Vincent, FB, et al. 2013, Ann Rheum Dis, Vol. 72, pp. 165-78.