Gloucestershire Hospitals
NHS Foundation Trust

Biologics Pathway for Severe Rheumatoid Arthritis (RA) in adults version2.0

This pathway has been produced primarily for use by the specialist Rheumatology Team. It aims to standardise the management of severe rheumatoid arthritis (RA) ensuring cost-effective evidence-based prescribing of biologics whilst reflecting the need for individual prescribing considerations.

In order to progress to this pathway, the patient must have:

- **tried at least TWO conventional disease modifying agents (cDMARDs) including Methotrexate (MTX)**
- **have severe disease with a disease activity score (DAS28) ≥ 5.1**

NICE have not assigned any hierarchical ranking to these therapies but have stated that treatment ***should be started with the least expensive drug, taking into account administration costs, dose needed and product price per dose.*** Therefore, the most cost-effective drug has been listed for each mode of action in the algorithm. Others that may be considered are listed in table 1, with pharmaceutical and clinical considerations that may be considered to support decision making.

- **Upon initiation continue treatment only if there is adequate response at 6 months after initiation of treatment measured using European League Against Rheumatology (EULAR) criteria or DAS28.**
- **After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.**
- ***Adequate response is defined as an improvement in DAS28 0.6 – 1.2 achieved in 6 months***
- ***If still active joint swelling and DAS28 ≥3.9 consider change in therapy***

Table of abbreviations:	
cDMARD	Conventional Disease Modifying Anti-Rheumatic Drug
bDMARD	Biologic Disease Modifying Anti-Rheumatic Drug
tsDMARD	Targeted- Synthetic Disease Modifying Anti-Rheumatic Drug
MTX	Methotrexate

Produced by: Farah Longerstaey, Dr G. Coombes
February 2024. Next Review due Feb 2026

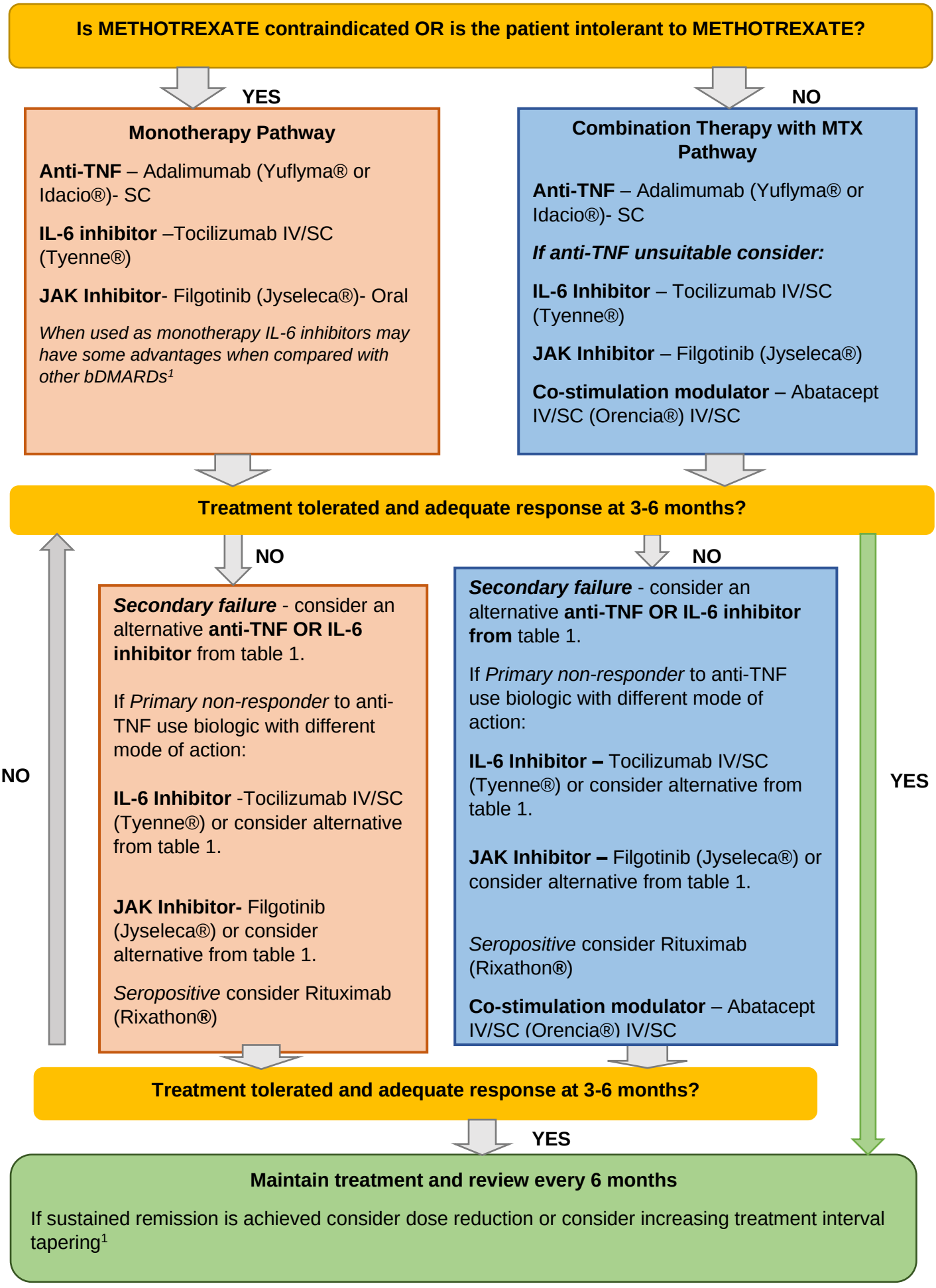

Table 1: NICE Approved biologics, listed in order of cost-effectiveness for each therapeutic class

Produced by: Farah Longerstaey, Dr G. Coombes
February 2024. Next Review due Feb 2026

Drug (Brand &/or approved Biosimilar)	***Suitable for Monotherapy?***	***Pharmaceutical Considerations***	***Clinical Considerations***
Anti-TNFs			
Adalimumab *(Yuflyma® or Idacio®)* *NICE TA375*	Suitable for both mono- and combination therapy	SC injection only Store in refrigerator Supplied via Homecare In monotherapy, the dose may be increased up to 40mg weekly for patients who have a decrease in response.	**Allergies:** Do not use if patient allergic to murine proteins and if patient has latex allergy **Contraindicated:** active severe infections, moderate or severe heart failure. **Cautions:** Demyelinating disorders, malignancy or history of malignancy, infections; sepsis or risk of sepsis. Haematologic reactions First line biologic if patient has co-existent IBD Consider in patients with extra-articular co-existent conditions such as uveitis, psoriasis Extensive data for use in pregnancy Cautioned for use in over 65-year-olds **Interactions:** Immunosuppressive drugs and Live vaccinations
Etanercept *(Benepali®)* *NICE TA375*	Suitable for both mono- and combination therapy	*SC injection* Store in refrigerator Supplied via Homecare	**Allergies:** Care in patients with latex allergy; contains rubber needle cover and plunger **Contraindicated:** active infection **Cautions:** Malignancy, diabetes mellitis, congestive heart failure, infections, blood disorders, demyelinating disorders, predisposition to septicaemia. Monitor blood sugars if diabetic patient; antidiabetic doses may need reducing Increased risk of infections in over 65-year-olds May be suitable option for patients experiencing secondary failure Extensive data for use in pregnancy **Interactions:** Immunosuppressive drugs and Live vaccinations

Infliximab *(Remsima®)* *NICE TA375*	Combination therapy only	*IV or SC injection* **Loading dose required** For IV therapy patient will be required to attend the Medical Day Unit (MDU) IV dose is weight-related **Subcutaneous Route** For SC route patient will require initial IV or SC loading dose and then must agree to Homecare therapy; patient must have access to fridge	**Allergies:** Do not use if patient allergic to murine proteins **Contraindicated:** Severe infection, moderate or severe heart failure **Cautions:** Demyelinating disorders, dermatomyositis, malignancy, mild heart failure, infection. Risk of delayed hypersensitivity reactions. Risk of antibody formation. Hepatitis, haematological reactions. Greater incidence of serious infections in patients aged 65 years **Interactions:** Immunosuppressive drugs and Live vaccinations
Golimumab *(simponi®)* *NICE TA375*	Combination therapy only	*SC injection* Store in refrigerator Supplied via Homecare Monthly injections on the same date each month. May be considered for those who are needle phobic as requires less frequent injections **Homecare nursing support unavailable** Patients with body weight >100kg who do not have adequate clinical response at 3-4 months can increase dose from 50 to 100mg	**Allergies:** Latex **Contraindicated***:* Severe active infections and moderate to severe heart failure. **Cautions:** Active infection, demyelinating disorders, malignancy, mild heart failure, predisposition to infection; dysplasia or carcinoma of the colon. Possible increased risk of infections in patients aged 65 and over.
Certolizumab pegol *(Cimzia®)* *NICE TA375*	Suitable for both mono- and combination therapy	*SC injection* Store in refrigerator Supplied via Homecare **Loading dose required**	**Allergies:** Latex **Contraindicated:** Severe infections, Moderate to severe heart failure. **Cautions***:* Demyelinating disorders; active infection, malignancy, mild heart failure, pre-disposition to infection, haematological reactions, Higher incidence of infections in patients aged 65years or over Extensive data for use in pregnancy Compatible with all 3 trimesters, has no to minimal placental transfer compared with other anti-TNF, and does not require alteration to the infant vaccination schedule[2]
IL-6 Inhibitors			
Tocilizumab *(Tyenne®)* *NICE TA375*	Suitable for both mono- and combination therapy	*IV route or SC injection* Patient must have access to fridge and agree to Homecare Therapy	**Contraindications:** Active severe infections (unless used for the treatment of COVID-19). Do not initiate if hepatic enzymes (ALT or AST) more than 5 times the upper limit of normal; do not initiate in patients not previously treated with *RoActemra®* if absolute neutrophil count less than 2 x 10^9/litre

			Cautions: Chronic or recurrent infection, predisposition to infection. Previous history of diverticulitis or intestinal ulceration Active hepatic disease or hepatic impairment Obtain baseline neutrophil, platelet and lipid levels prior to commencing therapy and monitor regularly. Monitor renal and hepatic function. Hepatic enzymes more than 1.5 times the upper limit of normal; low absolute neutrophil count; low platelet count Increased risk of dizziness can affect driving and operation of machinery. **Check interactions**: aminophylline, statins, calcium channel blockers, warfarin, phenytoin, live and attenuated vaccines and others. See BNF
Sarilumab *(Kevzara®)* *NICE TA485*	Suitable for both mono- and combination therapy	*SC injection* **Homecare nursing support unavailable** Patient must have access to fridge and agree to Homecare Therapy Dose reduction from 200mg every 2 weeks to 150mg every 2 weeks is recommended for management of neutropenia, thrombocytopenia and liver enzyme elevations. See SPC for details	**Contraindications:** Active, severe infections. Obtain baseline neutrophil and platelet count prior to commencing therapy and monitor regularly. Do not initiate if absolute neutrophil count less than 2 x 10^9/L; do not initiate if platelet count less than 150 x 10^3/µL; do not initiate if serum transaminases (ALT or AST) greater than 1.5 times the upper limit of normal **Cautions:** Chronic or recurrent infection; elderly (increased risk of infection); history of diverticulitis; history of diverticulitis or intestinal ulceration; history of serious or opportunistic infection; predisposition to infection. Obtain baseline lipid levels and monitor regularly Not recommended in patients with active hepatic disease or hepatic impairment Advise use of extra contraception if using combined hormonal contraception. **Check interactions**: statins; warfarin; combined hormonal contraceptive; xanthines, vaccinations and others. See BNF

JAK Inhibitors – Following recent MHRA update JAK-Inhibitors should not be used in patients with the following risk factors unless there are no suitable alternatives:

- **Aged 65 years or over**
- **patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers, diabetes, hypertension)**
- **patients with malignancy risk factors (e.g., current malignancy or history of malignancy)**
- **Use with caution when prescribing in patients with other risk factors for VTE and prescribe lower doses if possible.**
- **Carry out periodic skin examination on all patients to check for skin malignancy.**
- **Inform patients and their carers of these risks, and the signs and symptoms that warrant urgent medical attention**

Filgotinib (Jyseleca®) *TA676*	Suitable for both mono- and combination therapy	*Oral formulation* Recommended dose 200mg daily In patients over 65 years, in moderate / severe renal impairment and in adults at increased risk of VTE, MACE (major adverse cardiovascular events) and malignancy, the recommended dose is 100mg daily. It may be escalated to 200mg in case of insufficient disease control. For long term treatment, the lowest effective dose should be used	**Allergies:** Galactose intolerance, total lactase deficiency or glucose-galactose malabsorption. **Contraindications:** Active serious infection, pregnancy Absolute lymphocyte count less than 0.5 x 10^9 cells/litre; absolute neutrophil count less than 1 x 10^9 cells/litre; haemoglobin less than 80g/L **Cautions:** Avoid in those aged 65 years and older. History of serious or opportunistic infection, chronic or recurrent infection, predisposition to infection Risk of herpes reactivation Use with caution in patients with risk factors for DVT or PE; history of atherosclerotic cardiovascular disease or other cardiovascular risk factors risk factors Monitor renal function- Cautioned in moderate or severe impairment; avoid in end-stage renal disease. Avoid in severe hepatic impairment Interrupt treatment if absolute neutrophil count less than 1 x 10^9 cells/litre, absolute lymphocyte count less than 0.5 x 10^9 cells/litre, or haemoglobin less than 80g/L—treatment may be restarted when levels return above these values. • Monitor for signs and symptoms of infections • Monitor lipids; 12 weeks after treatment initiation and as needed thereafter. Hyperlipidaemia should be managed according to international clinical guidelines. • Monitor neutrophils, lymphocytes and haemoglobin

			• Periodic skin examination recommended. • Monitor hepatic transaminases. • Viral reactivation • Monitor renal function Females of childbearing potential should use effective contraception during and for at least 1 week after stopping treatment. **Also licensed for ulcerative colitis** **Interactions:** Other immunosuppressant drugs and live vaccines. See BNF **Also licensed for ulcerative colitis**
Baricitinib (Olumiant®) *TA466*	Suitable for both mono- and combination therapy	*Oral formulation* Recommended dose is 4mg daily A dose of 2mg daily is recommended for patients aged 65 and older, patients at higher risk of VTE, MACE and malignancy, history of chronic or recurrent infection, renal impairment. A dose of 4mg may be considered for those patients who do not achieve adequate disease control.	**Contraindications:** Pregnancy. Absolute lymphocyte count less than 0.5 x 10^9 cells/litre; absolute neutrophil count less than 1 x 10^9 cells/litre; haemoglobin less than 80g/L; Active tuberculosis **Cautions:** Active, chronic, or recurrent infection; history of atherosclerotic cardiovascular disease or other cardiovascular risk factors; risk factors for deep-vein thrombosis or pulmonary embolism; risk factors for malignancy; risk of diverticulitis; risk of viral reactivation. Renal impairment CrCl < 30mls/min Severe hepatic impairment Avoid in those aged 65 years and older. • Monitor for signs and symptoms of infections • Monitor lipids; 12 weeks after treatment initiation and as needed thereafter. Hyperlipidaemia should be managed according to international clinical guidelines. • Monitor neutrophils, lymphocytes and haemoglobin • Periodic skin examination recommended. • Monitor hepatic transaminases. • Viral reactivation • Monitor renal function Females of childbearing potential should use effective contraception

			during and for at least 1 week after stopping treatment. **Check interactions:** Other immunosuppressant drugs & live vaccines. See BNF **Also licensed for Atopic Dermatitis and Alopecia Areata**
Upadacitinib (Rinvoq®) *NICE TA665*	Suitable for both mono- and combination therapy	*Oral formulation* Rheumatoid Arthritis dose 15mg daily	**Contraindications:** Pregnancy Severe hepatic impairment Active serious infection; absolute lymphocyte count less than 0.5 x 10^9 cells/litre; absolute neutrophil count less than 1 x 10^9 cells/litre; haemoglobin less than 80g/L **Cautions:** Not recommended in over 65-year-olds. History of atherosclerotic cardiovascular disease or other cardiovascular risk factors; malignancies. Risk of diverticulitis or GI perforation (investigate new onset abdominal signs and symptoms promptly); malignancy risk factors; chronic, recurrent or history of serious infection; risk of viral reactivation; risk factors for VTE or PE. Severe renal impairment • Monitor for signs and symptoms of infection during and after treatment • Monitor neutrophils, lymphocytes and haemoglobin • Periodic skin examination recommended. • Monitor hepatic transaminases. • Monitor renal function • Viral hepatitis reactivation Risk of hypoglycaemia in patients receiving medication for diabetes; dose adjustment may be necessary **Check interactions:** Antivirals; anti-fungals; anti-epileptics; live vaccines, immunosuppressants. Avoid grapefruit See BNF. **Also licensed for Ulcerative Colitis, Crohn's disease, Atopic Dermatitis**
Tofacitinib *(Xeljanz®)* *NICE TA480*	Suitable for both mono- and combination therapy	*Oral formulation*	**Contraindications:** Pregnancy, Active severe infections; active tuberculosis, severe hepatic impairment.

			Absolute lymphocyte count less than 750 cells/mm^3 (do not initiate); Absolute neutrophil count less than 1000 cells/mm^3 (do not initiate); Haemoglobin less than 90g/L (do not initiate). Not suitable for patient at risk of VTE; carry out VTE risk assessment before prescribing. Inform patients of the signs and symptoms of VTE before starting treatment. **Cautions:** Not recommended in over 65-year-olds. Avoid in patients with increased risk of cardiovascular events and malignancies. Fracture Risk, Risk of diverticulitis or GI perforation (investigate new onset abdominal signs and symptoms promptly); malignancy risk factors; recurrent or history of serious infection; risk factors for VTE; risk of viral reactivation e.g., herpes zoster. Interstitial lung disease. • Monitor for signs and symptoms of infection during and after treatment. • Monitor neutrophils, lymphocytes and haemoglobin. • Monitor hepatic transaminases. • Monitor renal function • Lipid monitoring and management according to clinical guidelines • Periodic skin examination recommended Risk of hypoglycaemia in patients receiving medication for diabetes; dose adjustment may be necessary **Check interactions**: anti-bacterials; anti-epileptics; anti-fungals, anti-virals; immunosuppressants; live vaccines, warfarin. See BNF **Also licensed for Ulcerative Colitis, Psoriatic arthritis. Ankylosing spondylitis.**
B-cell depletor			
Rituximab *(Rixathon®)* *NICE TA195*	YES – if seropositive	*IV administration only*, must attend MDU for administration.	**Contraindicated:** Severe active infection. Severe heart failure, severe uncontrolled cardiac disease. **Cautions:**

		May be considered a first line biologic option in patients with previous malignancy or pre-malignant conditions[3] Rituximab or abatacept may be considered a first line biologic in patients with interstitial lung disease[3] Recommended that immunoglobulin (IgG) levels are checked before initiation and prior to each cycle of treatment.[3]	History of cardiovascular disease (exacerbation of angina, arrhythmia, and heart failure have been reported) Chronic or recurrent infection Predisposition to infection Warn patients of potential increased risk of progressive multifocal leukoencephalopathy (PML) Transient hypotension occurs frequently during infusion (anti-hypertensives may need to be withheld for 12 hours before infusion). Pre-medication recommended to minimise adverse reactions to minimise infusion related side-effects. **Interactions:** live vaccines and immunosuppressant drugs. See BNF. Reduces response to COVID vaccination
Co-stimulation modulator			
Abatacept *(Orencia®)* *NICE TA375*	NOT suitable for monotherapy	*IV or SC administration* Rituximab or abatacept may be considered a first line biologic in patients with interstitial lung disease[3]	**Contra-indications:** Severe infections **Cautions:** Do not initiate until active infections are controlled; elderly (increased risk of side effects); history of recurrent infection, predisposition to infection. Screen for latent tuberculosis and viral hepatitis. Progressive multifocal leukoencephalopathy (discontinue treatment if neurological symptoms suggestive of PML develop). Malignancies **Interactions:** Live vaccines and immunosuppressant drugs. *Periodic skin examinations recommended*

Useful links:

Principles for COVID-19 Vaccination in Musculoskeletal and Rheumatology for Clinicians COVID-19 vaccination and MSK (arma.uk.net)

British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory and anti-rheumatic drugs and corticosteroids OP-BRHE220553 48..88 (silverchair.com)

The Handbook of Perioperative Medicines UKCPA The Handbook of Perioperative Medicines (ukcpa-periophandbook.co.uk)

References:

1. Smolen JS. Landewé RBM. Bergstra SA. Kerschbaumer A. *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Disease 2022. [Accessed via EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update (bmj.com) 13/02/2024]

2. Russell MD. Dey M. Flint J. Davie P *et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids.* Rheumatology 2022 [Accessed via OP-BRHE220553 48..88 (silverchair.com) 12/02/2024]

3. Holroyd Cr. Seth R. Bukhari M. *et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis – Executive summary.* Rheumatology2019;220-226 [Accessed via British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis—Executive summary | Rheumatology | Oxford Academic (oup.com) 20/02/2024]

Table 2. Record of changes

Date	Changes Made	Changes made by
09/04/2024	*Record of changes table added*	*FL*
09/04/2024	*Tocilizumab brand switched to Tyenne® biosimilar*	*FL*
18/11/2024	*Adalimumab brand names updated as Hyrimoz® withdrawn from UK market*	*FL*

Produced by: Farah Longerstaey, Dr G. Coombes
February 2024. Next Review due Feb 2026