YORKSHIRE RHEUMATOLOGY REGIONAL GUIDELINES FOR THE MONITORING OF ADULT PATIENTS ON CONVENTIONAL DISEASE MODIFYING DRUGS, BIOLOGIC DRUGS AND TARGETED SYNTHETIC DRUGS

7th Edition

Revised March 2019

1. Introduction

The above group of Rheumatologists have, after extensive discussion with reference to the published literature, agreed upon these guidelines. There has been recent BSR safety guidance (2016 and 2017) on the use of biologics, which has been incorporated. These Yorkshire Guidelines are felt to represent a safe level of clinical care for patients requiring DMARD treatment, while keeping monitoring time and expenditure to an acceptable level. Initial assessment of patients and the decision to start treatment will continue to be carefully made by Consultants and GPs where appropriate. For each drug a single reference sheet outlining recommended drug monitoring tests, which should be done in order to minimise the risk of toxicity, is enclosed. These have been standardised where possible to allow consistency and reduce errors. A link is provided to the electronic compendium of datasheets to allow the prescriber to access additional detailed information on contra-indications, side effects and drug interactions for both synthetic and biologic DMARDs (http://www.medicines.org.uk/emc/).

Under most circumstances, csDMARD drug monitoring and prescribing is best undertaken in General Practice after initiation and on stable therapy. This is requested by patients and is felt to improve compliance. Monitoring should be in agreement with locally agreed Shared Care Guidance. Where patients have severe disease and more toxic drug regimens, hospital monitoring in the initial stages will usually be preferred. Where possible a hospital based rheumatology specialist nurse will be available for advice for patients or medical staff regarding problems with the use of these drugs. Consultant Rheumatologists are also contactable by telephone, fax or email for advice when needed.

We would like to acknowledge Tina Hawkins, specialist pharmacist, who initiated the first draft. We also acknowledge Dr Gui Tran and Dr Andrew Gough, who have revised and produced these Guidelines.

These guidelines have now been revised 7 times and will continue to require modification. They are dated and will be reviewed in 2022. Suggestions for additions or alterations may be forwarded to:

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2. Abbreviations

ALC	Absolute Lymphocyte Count
ANC	Absolute Neutrophil Count
bDMARD	Biologic DMARD
C/I	Contraindications
CrCl	Creatinine clearance
csDMARD	Conventional synthetic DMARD
Nr	Non radiographic
SPC	Summary Product Characteristics
tsDMARD	Targeted synthetic DMARD
ULN	Upper Limit of Normal

3. Corticosteroids

Corticosteroids are commonly used in the management of a number of rheumatological conditions. Despite their known benefits, prolonged treatment can be associated with a number of detrimental side effects. EULAR guidance recommends that the adverse effects of glucocorticoid therapy should be considered and discussed with the patient before glucocorticoid therapy is started (Duru et al. 2013). Risk factors for adverse events include hypertension, diabetes, peptic ulcer, recent fracture, presence of cataract or glaucoma, presence of chronic infections, dyslipidaemia and co-medication with NSAIDs. For prolonged treatment, the dosage should be kept to a minimum and dose tapering attempted in cases of remission or low disease activity. Continued prescribing should be reviewed at regular intervals. The patient should be advised to take the tablets in the morning with or after food. Alternate day dosing, especially with long half-life NSAIDs, may be deemed appropriate to try and reduce side effects.

Immunosuppression: Prolonged courses of corticosteroids can increase the susceptibility to infection. Immune status with regards to chickenpox can be checked when indicated. Those patients who are not immune should avoid close contact with people who have chickenpox or shingles. If exposed the patient should be advised to contact their Doctor promptly for advice.

Adrenal suppression can occur if corticosteroids are given for longer than 3 weeks or the patient has received several repeat courses. Under these circumstances the dose of the corticosteroid should be gradually tapered. The speed and magnitude of reduction should be tailored according the patient's disease status and additional co-morbidities. All patients receiving prolonged treatment with corticosteroids should be issued with a "BLUE STEROID CARD", which can be obtained from both hospital and community pharmacies. The card should state the date treatment was commenced, the initial dosage, subsequent reductions and maintenance doses. Patients should be advised to carry the card with them and present it to Healthcare professionals in the case of illness. Where surgery is indicated, and the patient has been receiving treatment with glucocorticoids for over 1 month, it may be necessary to increase the glucocorticoid dose. The need for routine monitoring should be considered according to the dose, duration of treatment and the presence of pre-existing risk factors such as obesity, diabetes and cardiovascular disease.

Live vaccination: DOH guidance (Green Book) suggests delaying live vaccination for at least three months in adult patients who have received at least 40mg of prednisolone per day for more than 1 week or >20mg for >2 weeks . Individuals receiving prolonged oral corticosteroid treatment at lower doses may also be at risk. Please contact the Rheumatologist if live vaccination is being considered.

Osteoporosis: Patients on doses of greater than 7.5mg of prednisolone per day, who are likely to need treatment for more than 3 months, should be considered for bone protection therapy. Patients at high risk (including previous risk fracture, >65 etc) should start an oral bisphosphonate at the time of commencing steroid therapy usually with determination of bone mineral density status. The need for continuing bisphosphonate therapy, and possibly newer treatment options, should preferably be evaluated by a DEXA scan and according to individual patient risk factors. Physicians should refer to the appropriate clinical guideline (Osteoporosis - Clinical Guideline for Prevention and Treatment, Executive Summary June 2017, National Osteoporosis Guideline Group).
Where patients do not have adequate calcium intake in their diet, supplements should be considered (usually from over the counter). Similarly, where appropriate, over the counter vitamin D (1000 units daily) should be recommended for patients to obtain from pharmacies or supermarkets.

Pregnancy: Low dose glucocorticoids may be continued during pregnancy. Please contact the Rheumatologist if a female patient is receiving oral corticosteroids and is planning to conceive.

4. Synthetic or csDMARDs

Azathioprine

Dose:	Treatment is usually started at one 50mg tablet daily with or after breakfast for the first week. Subsequently, if no problems occur, the dose is usually increased weekly to 100mg daily and then 150mg daily, taken at the same time or in divided doses with meals. The dose is usually increased up to 2.5mg/kg per day and occasionally more if needed.
Baseline Tests:	FBC/U&E/LFT TPMT is recommended Consider Hepatitis B and C
Routine Monitoring:	FBC, U&Es, LFTs every 2 weeks until on stable dose for 6 weeks Once on stable dose, monthly for 3 months Thereafter, at least every 12 weeks. More frequent monitoring is appropriate in patients at higher risk of toxicity, or when clinically indicated (see below) Dose increases should be monitored by FBC, U&Es every 2 weeks until on stable dose for 6 weeks then revert to previous schedule
Indications for stopping:	Stop medication and contact the Rheumatology service if: Neutrophils < 1.6 x $10^{9/}$L or below local normal range Platelets <140 x$10^{9/}$L or below local normal range AST or ALT > 3 times normal range (iu/L) Mouth or throat ulceration Unexplained bruising or bleeding Fever/nausea/vomiting/diarrhoea & in presence of active infection Diffuse alopecia
Assessment of Response:	Refer to hospital specialist - time to response 6 weeks to 3 months
Additional information:	• Patients deficient in thiopurine methyltransferase (TPMT) enzyme are at increased risk of haematological toxicity • Renal or hepatic dysfunction – consider need for dose reduction to avoid haematological toxicity. • Consider check Varicella Zoster Virus status • Surveillance for skin cancer - monitoring of skin for any new lesions and/or changes. Provide advice on sunscreen and protective clothing. Those expected to remain on long term therapy (6-12 months) should be considered for dermatological screening annually. <u>Important drug reactions:</u> ●Allopurinol, oxypurinol and thiopurinol - reduced elimination of azathioprine and 6-mercaptopurine, reduce dose by one quarter of original dose. ● Warfarin - reduced anticoagulant effect. ●Captopril and possibly other ACE inhibitors - increased risk of myelosuppression. ● Co-trimoxazole and trimethoprim - increased risk of myelosuppression. ●Clozapine - increased risk of agranulocytosis. ●Sulfasalazine, mesalazine and olsalazine - possible increased risk of leucopenia.
Pregnancy & Breastfeeding:	Refer to Section 9 (Guidance on use of DMARDS in pregnancy)
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/2881/SPC/Imuran+Tablets+25mg/	

Cyclosporine

Dose:	RA usual starting dose of 1-2mg/kg daily in 2 divided doses for 6 weeks. Then small 25mg incremental increases in dose 2 weekly until clinically effective or maximum dose 3-4mg/kg or toxicity occurs (increase in Creatinine/Potassium). (Refer to datasheet for dosage reduction in patients with increasing creatinine levels)
Baseline Tests:	Clinical examination including blood pressure and urinalysis FBC/U&E/LFT/Urate/Lipids + consider pregnancy test Note 24 hour urine CrCl or PCI and GFR is suggested
Routine Monitoring:	Blood pressure (with each blood test) U&Es/LFTs 2 weekly until stable dosage reached Then monthly for 4 months, then 3 monthly Check lipids/urate at 2-3 months (optional) Dose increases should be monitored by FBC, U&Es and LFTs every 2 weeks until on stable dose for 6 weeks then revert to previous schedule
Indications for Stopping:	Stop medication and contact the rheumatology service if: BP >160/95 or risen >20mmHg Potassium >5.5mmol/l (especially with ACEi) Neutrophils < 1.6 x $10^{9/}$L or below local normal range Platelets <140 x$10^{9/}$L or below local normal range AST or ALT > 3 times normal range (iu/L) If creatinine clearance 30% or more below baseline, reduce dose or stop Ankle swelling/Headache (check BP)/ Tremor/gingival hyperplasia/ hirsutism/confusion
Additional Information:	Contra-indications - abnormal renal function, uncontrolled hypertension, uncontrolled infections and malignancy. Generic formulations are now available – confirm preparation before prescribing. <u>Important drug reactions:</u> •**Drugs which decrease ciclosporin levels (CYP3A4):** Barbiturates, carbamazepine, oxcarbazepine, phenytoin; nafcillin, intravenous sulfadimidine, probucol, orlistat, ticlopidine, sulfinpyrazone, terbinafine, bosentan. •**Drugs which increase ciclosporin levels (CYP3A4):** Macrolide antibiotics, azole antibiotics, amiodarone, diltiazem, verapamil, nicardipine, metoclopramide, oral contraceptives, methylprednisolone (high dose), allopurinol, cholic acid and derivatives, protease inhibitors, imatinib, colchicine, nefazodone. •**NSAIDS** - increased risk of abnormal LFTs in patients taking NSAIDs (Note the dose of diclofenac should be decreased by 50%). •Statins – Confirm the need for dose reduction or avoidance of certain statins (<u>avoid simvastatin and rosuvastatin</u>) in accordance with the licensed datasheet. •Digoxin and colchicine - reduced clearance •St John's Wort - significantly decreases ciclosporin levels and should be avoided. •**Grapefruit and grapefruit juice** - avoid an hour before and after taking ciclosporin. •Live vaccines should not be given - refer to the vaccine section for more detailed information
Pregnancy & Breastfeeding:	Refer to Section 9 (Guidance on use of DMARDS in pregnancy)
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/22945/SPC/Deximune+25mg%2c+50mg%2c+100mg+Capsules/	

Cyclophosphamide

Dose:	The regimen varies according to the clinical indication and co-morbidities. An example of one current regime is: 10-15mg /kg IV Cyclophosphamide + 2.5 - 10mg/kg IV methylprednisolone 3 pulses given 2 weekly, then 3 given 3 weekly Oral mesna should be given in conjunction with cyclophosphamide: 400mg orally 2 hours before, 2 hours after and 6 hours after. However, the risk of haemorrhagic cystitis is deemed to be low with current standard dosage regimes used in rheumatology. Although not highly emetogenic some patients may require pre-treatment with an anti-emetic. A high fluid intake should be encouraged on the day of administration.
Baseline tests:	FBC/U&E/LFT Urinalysis Consider pregnancy test
Routine Monitoring:	FBC to be performed 10 days after each pulse (nadir result) Urinalysis Neutrophils < 1.6 x $10^{9/}$L or below local normal range (a nadir of less is fine, provided recovery before the next dose) Platelets <140 x$10^{9/}$L or below local normal range AST or ALT > 3 times normal range (iu/L) Plus repeat blood results immediately prior to giving next pulse.
Indications for stopping:	Contact local rheumatology service if: Neutrophils < 1.6 x $10^{9/}$L, Platelets <140 $10^{9/}$L Oral ulceration/unusual bruising/rash/fever/cough or shortness of breath/nausea/alopecia
Assessment of response:	Defined by the Rheumatology Consultant according to the disease/organ(s) affected. An interim review should be performed after the first 3 pulses and full assessment after completion of 6. Pulse therapies may be considered in some cases with further spacing intervals
Additional information:	Infection to be excluded before administration of each infusion. Consider PCP prophylaxis if longer term treatment being used **CAUTION:** Porphyria Previous haematological abnormality History or recurrent infection Renal or hepatic impairment Hypersensitivity Haemorrhagic cystitis Urinary incontinence/ recurrent urinary tract infection/catherisation **Drug Interactions:** AVOID live vaccines Other immunosuppressants Not with clozapine Oral hypoglycaemics may be potentiated by cyclophosphamide.
Pregnancy & Breastfeeding:	Refer to Section 9 (Guidance on use of DMARDS in pregnancy)
Refer to the Rheumatologist and the Hospital Medicines Information Department for more detailed prescribing information.	

Injectable gold (sodium aurothiomalate)

Dose:	RA - An initial 10mg intra-muscular test dose should be given in the first week followed by a maintenance dose of 50mg by intra-muscular injection the following week and then weekly. Patients should be monitored for 30 minutes following each dose. FBC and urine should be checked before each injection. Frequency of injections can be reduced according to response to once every 4 - 8 weeks.
Baseline Tests:	• FBC • U&E • LFT • Urinalysis • Baseline chest X-ray (consider annual repeat) Inform patient to report – pruritis, metallic taste in the mouth, sore throat or tongue, buccal ulceration, easy bruising, purpura, epistaxis, bleeding gums, inappropriate menstrual bleeding or diarrhoea.
Routine Monitoring:	• FBC and Urinalysis at the time of each injection (Provided blood results are stable. The results of the FBC need not be available before the injection is given but must be available before the next injection (i.e. it is permissible to work one FBC in arrears). FBC frequency may be reduced to >6 monthly in long term stable users. • Urinalysis must be done before each injection.
Indications for Stopping Therapy:	**Note:** Anaphylactic reaction may occur at any stage of treatment and usually occurs within the first 10 minutes of administering the injection. If the patient develops sore throat, glossitis, buccal ulceration, easy bruising, a rash or bleeding perform an immediate blood test. If any of the following occur, **stop treatment** and contact the hospital specialist: Neutrophils < 1.6 x $10^{9/}$L or below local normal range Platelets <140 x$10^{9/}$L or below local normal range Proteinuria/Blood >1+ (Where protein is detected do MSU and if negative perform a urine PCI / PCR (or 24 hour urine collection for protein and creatinine clearance). If blood tests are normal despite the above symptoms, stop treatment for 1-2 weeks (until symptoms disappear) and consider re-challenge with test dose (consult hospital specialist).
Assessment of Response:	If after reaching a total dose of 1g (excluding test dose), no major improvement has occurred the Specialist will usually discontinue therapy.
Additional information:	Contra-indicated - Gross renal or hepatic disease, history of blood dyscrasias, exfoliative dermatitis and systemic lupus erythematosus (SLE). Important drug reactions: • Penicillamine (increased risk of rashes and bone marrow depression) • Aspirin (increased risk of aspirin-induced hepatic dysfunction) • ACE inhibitors (increased risk of severe anaphylactoid reactions)
Pregnancy & Breastfeeding:	Avoid in pregnancy and breastfeeding as safety has not been established.
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/18613/SPC/Myocrisin+100mg+ml+Solution+for+Injection/	

Hydroxychloroquine

Dose:	Considered for treatment of rheumatoid arthritis, juvenile idiopathic arthritis, systemic lupus erythematosus and other CTDs Usually started at a dose of 200mg bd for the first 3 months and then reduce to 200mg daily as a maintenance dose if effective (aim for 3-5mg/kg/day using ideal bodyweight especially where patients are obese)
Baseline tests:	Baseline blood/urine monitoring test: • FBC/U&E/LFT • Baseline optician assessment Full ophthalmological screening within first year of treatment and annually if **high** risk: • ≥5mg/kg/day • SLE • Impaired renal function (eGFR<30) • If concurrent use of tamoxifen • If using chloroquine at any dose Full ophthalmological screening after 3 years if **low** risk (<5mg/kg/day and none of the above), and then at 5 years: = the baseline assessment Initial ophthalmological screening includes: fundus photography and macular OCT Not generally recommended where pre-existing maculopathy.
Routine monitoring:	Renal function annually in over 70's or if pre-existing renal impairment or when known hypertension / diabetes Optician screening: recommend pre-treatment assessment and then annual unless formal ophthalmological screening is undertaken (in years 1, 2 and 4 in low-risk patients) Routine ophthalmology monitoring for: High risk screening = annually from year 1 Low risk starts from 5 years and continues annually
Indications for stopping therapy:	**Stop medication and contact local rheumatology service if:** Photophobia/Haloes/Visual field defects/reduced acuity/abnormal colour vision/ pigmentary abnormality/ muscle weakness Not considered a risk factor for infection so safe to continue
Assessment of Response:	For rheumatic disease treatment should be discontinued if there is no significant improvement by 4-6 months.
Additional information:	Use in caution in patients with: • Psoriasis - increased risk of flare • Patients taking medicines which may cause adverse ocular/skin reactions • Patients with quinine sensitivity. **Severe hypoglycaemia** has been reported, even in the absence of anti-diabetic medication. Hepatic or renal disease, and in those taking drugs known to affect those organs - dosage adjusted accordingly (seek advice from Pharmacy) Important drug interactions: amiodarone, moxifloxacin, ciclosporin, digoxin Antacids (advise a 4 hour interval)
Pregnancy & Breastfeeding:	Refer to Section 9 (Guidance on use of DMARDS in pregnancy)
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/6977/SPC/Plaquenil+Tablets/	

Leflunomide

Dose:	Usually considered for patients with active RA/ PsA/vasculitis who have failed methotrexate and/or sulphasalazine. Loading dose of 100mg daily for three days IS NOT recommended 10-20 mg daily as a single tablet should be used. Timing of dose is not important. Patients with uncertain alcohol intake or other hepatotoxic drugs may warrant increased vigilance.
Baseline tests:	FBC/U&E and LFT BP Consider Pregnancy test Consider Chest X-ray and PFTs Consider Hep B/C/ HIV Note: use is contra-indicated in hepatic impairment, severe immunodeficiency states (AIDS), moderate to severe renal impairment, severe hypoproteinaemia (nephrotic syndrome) and impaired bone marrow function.
Routine monitoring:	BP at each visit FBC, U&Es, LFTs every 2 weeks until on stable dose for 6 weeks Once on stable dose, monthly for 3 months Thereafter, at least every 12 weeks. More frequent monitoring is appropriate in patients at higher risk of toxicity, or when clinically indicated Dose increases should be monitored by FBC, U&Es and LFTs every 2 weeks until on stable dose for 6 weeks then revert to previous schedule
Indications for stopping treatment:	• Ulcerative stomatitis – stop and contact specialist • Skin/mucosal reaction (risk of Stephen Johnson) – stop and contact specialist (washout recommended – cholestyramine 8g tds for 11 days or charcoal). • Peripheral neuropathy – consider stop and contact hospital specialist. In addition, Stop medication and hospital specialist if : • Neutrophils < 1.6 x $10^{9/}$L or below local normal range • Platelets <140 x$10^{9/}$L or below local normal range • AST or ALT > 3 times normal range (iu/L) • Significant BP rise or > 160/95 • Abdominal pain/Nausea/Diarrhoea/Weight loss/Pruritis/Rash/ • Breathlessness or infection - perform CXR +/- PFT
Assessment of Response:	Clinical effect usually within 2 to 4 months.
Additional information:	Can be associated with pulmonary toxicity (?more in East Asian Groups) Avoidance of alcohol recommended Important drug interactions: hepatoxic/haemotoxic drugs, cholestyramine, rifampicin, warfarin, tolbutamide and phenytoin. Contains lactose and soya lecithin – avoid in lactose, soya or peanut allergy. Infusion reactions may be increased when combined with infliximab
Pregnancy & Breastfeeding:	Refer to Section 9 (Guidance on use of DMARDS in pregnancy)
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/7480/SPC/Arava+10%2c+20+and+100mg+Tablets/	

Methotrexate

Dose:	Treatment may begin at a dose of 10-20mg WEEKLY using 2.5mg tablets and increased to 20mg after 2-4 weeks. Folic acid should be co-prescribed, but patients should be advised not to take it on the day they take their methotrexate. The day of administration plus strength of tablet should be specified. Consider changing to the subcutaneous route if there is gastric intolerance or a lack of efficacy at the higher end of the dose range. Maximum recommended dose oral or SC = 30mg weekly.
Baseline Tests:	FBC/U&E/LFT Consider pregnancy test All patients should have a pre-treatment CXR and consider PFT (in RA). Where TLCO less than 70% or clinical concern a baseline HRCT chest may be advisable (lung toxicity may be increased when fibrosis is present)
Routine Monitoring:	FBC and LFTs every 2 weeks until on stable dose for 6 weeks Once on stable dose, monthly for 3 months and then every 3 months Patients at risk of renal impairment may need U&Es checked regularly or if not annually More frequent monitoring is appropriate in patients at higher risk of toxicity, or when clinically indicated. NPSA still recommend MTX monitoring books for patients Dose increases should be monitored by FBC and LFTs at 2 and 6 weeks and then every 3 months
Indications for Stopping Therapy:	**Stop medication and contact local rheumatology service if:** Neutrophils < 1.6 x $10^{9/}$L or below local normal range Platelets <140 x$10^{9/}$L or below local normal range AST or ALT > 3 times normal range (iu/L) Oral ulceration/Unusual bruising/Rash/Nausea/Alopecia Any new respiratory symptoms including cough Fever **Consider the need for folinic acid rescue - refer to BNF for dosage recommendations and discuss with Rheumatology Service**
Assessment of Response:	Clinical effect usually within 2 to 4 months.
Additional information:	**Warnings/Caution:** Avoid in significant hepatic impairment Not recommended in severe renal impairment (creatinine clearance <10ml/min) the dose should be reduced by 50% if the CrCl is between 10-20ml/min. Also consider dose reduction if CrCl 20-50ml/min. Pre-existing haematological condition Underlying chest disease Where history of excessive alcohol intake **Drug interactions:** Concomitant administration of folate antagonists such as trimethoprim and nitrous oxide should be avoided. Use of co-trimoxazole may occur in patients with GPA, under specialist supervision Penicillins may potentiate levels of methotrexate (Patients should stop taking methotrexate if they have any infection/require antibiotics, and restart once the antibiotic course is completed / the infection has resolved) Acitretin - severe hepatitis reported when combined with MTX Vitamin preparations containing folic acid
Pregnancy & Breastfeeding:	Refer to Section 9 (Guidance on use of DMARDS in pregnancy)
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/6005/SPC/Maxtrex+Tablets+10+mg/	

Mycophenolate mofetil

Dose:	In connective tissue disease – usual starting dose is 500mg twice daily for 2 weeks and then 1g twice daily. If there is gastric intolerance consider giving as 500mg four times a day. If indicated the dose may be increased to 1.5g twice a day. **Renal impairment:** If GFR <25ml/min commence on 250mg bd and gradually titrate, not exceeding 1g bd. Note: The dose of mycophenolic acid (Myfortic®) is not equivalent; 720mg of mycophenolic acid is approximately equivalent to 1g of mycophenolate mofetil. Where possible, maintain the same generic when prescribing
Baseline tests:	FBC/U&E/LFT/lipids and BP Consider Hepatitis B/C/HIV Varicella immune status (avoid if re-current herpes/shingles) Consider Pregnancy Test
Routine monitoring:	FBC, U&Es, LFTs every 2 weeks until on stable dose for 6 weeks Once on stable dose, monthly for 3 months Thereafter, at least every 12 weeks. More frequent monitoring is appropriate in patients at higher risk of toxicity, or when clinically indicated Dose increases should be monitored by FBC and LFTs at 2 and 6 weeks and then revert to previous schedule Consider measure serum immunoglobulin levels intermittently or if recurrent infections develop Consider bronchiectasis or pulmonary fibrosis if patients develop persistent respiratory symptoms.
Indications for stopping therapy:	Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding. Perform an immediate blood test and stop medication and contact local rheumatology service if: Neutrophils < 1.6 x $10^{9/}$L or below local normal range Platelets <140 x$10^{9/}$L or below local normal range AST or ALT > 3 times normal range (iu/L)
Assessment of response:	Usually at 3-4 months and defined by the Rheumatology Consultant according to the disease/organ affected
Additional information:	Advise patients to minimise exposure to sunlight and wear sunscreen with a high protection factor. Avoid in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome. Gastric side effects can occur including ulceration, perforation and haemorrhage. <u>Important drug interactions:</u> Avoid concomitant use with azathioprine, aciclovir/ganciclovir and probenecid. The following decrease levels: antacids , proton pump inhibitors, cholestyramine, norfloxacin/metronidazole, ciprofloxacin/co-amoxiclav and rifampicin.
Pregnancy & Breastfeeding:	Refer to Section 9 (Guidance on use of DMARDS in pregnancy)
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/1679/SPC/Cellcept+250mg+Capsules/ https://www.gov.uk/drug-safety-update/mycophenolate-mofetil-cellcept-and-mycophenolic-acid-risk-of-hypogammaglobulinaemia-and-risk-of-bronchiectasis	

Penicillamine

Dose:	Treatment is usually started at 125mg daily taken at least half an hour before food/milk or last thing at night. If no problems occur the dosage may be increased to : • 250mg tablet daily for 1 week • 375mg daily for 1 week • Then two 250mg tablets daily 500mg daily in divided doses for 3 months is recommended. Further increases may be necessary if limited clinical response, with a usual maximum of 750mg daily (rarely more). Consider co-administration of pyridoxine if treatment is continued long term.
Baseline Tests:	Urinalysis FBC/U&E
Routine Monitoring:	Two weekly for the first 2 months (0-2 months) Monthly for 4 months (2-6 months) Thereafter 3 monthly (unless dose changes)
Indications for Stopping Therapy:	Stop and contact local rheumatology service if : • Neutrophils < 2.0 10^{9}/L or local normal range • Platelets <150 10^{9}/L or local normal range • Proteinuria/Blood >1+ Rash - Antihistamines/steroid cover/temporary reduction in dose can control uticarial rash. Unusual bruising/mouth ulceration/loss of taste. If proteinuria and negative MSU, suggest PCI and GFR (or 24 hour urine for CrCl and protein)
Assessment of Response:	4-6 months
Additional information:	**Contra-indicated when:** • SLE • Previous agranulocytosis, aplastic anaemia or severe thrombocytopenia in association with penicillamine • Moderate or severe renal impairment **Drug interactions:** • Concomitant use of NSAIDs and other nephrotoxic drugs may increase the risk of renal damage. • Penicillamine should be used with caution in patients who have had adverse reactions to gold. • If concomitant oral iron, digoxin, zinc or antacid therapy is indicated, this should not be given within two hours of taking penicillamine.
Pregnancy & Breastfeeding:	Please contact the Rheumatologist if patient considering conceiving or in case of pregnancy.
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/emc/medicine/9211/SPC/Distamine+125mg+Film-coated+tablets/	

Sulfasalazine

Dose:	Indications include - Rheumatoid arthritis, psoriatic arthritis and IBD related arthritis Gradual dose titration to avoid gastric intolerance (enteric coated prep may be considered) e.g. 500mg BD for 2 weeks, then 1g twice a day. If gastric intolerance consider 500mg four times a day. If indicated the dose may be increased to 1.5g twice a day.
Baseline tests:	FBC LFTs U&E Consider serum folate
Routine monitoring:	FBC, U&Es, LFTs every 2 weeks until on stable dose for 6 weeks; then once on stable dose, monthly for 3 months; thereafter, at least every 12 weeks. More frequent monitoring is appropriate in patients at higher risk of toxicity, or when clinically indicated Dose increases should be monitored by FBC and LFTs at 2 and 6 weeks and then revert to previous schedule Monitoring may be discontinued after 1 year on direct consultant guidance
Indications for Stopping Therapy:	The patient should be counselled to report immediately with any sore throat, fever, malaise, pallor, purpura, jaundice or unexpected non-specific illness during sulfasalazine treatment (interrupt therapy and perform a blood test). Stop medication and contact local rheumatology service if: • Neutrophils < 1.6 x $10^{9/}$L or below local normal range • Platelets <140 x$10^{9/}$L or below local normal range • AST or ALT > 3 times normal range (iu/L) Generally not considered a risk factor for infection so remains safe to continue
Assessment of response:	At 3-6 months
Additional information:	• Contra-indicated in patient with hypersensitivity to sulphonamides or salicylates. • Contra-indicated in Porphyria • Avoid in hepatic and/or renal impairment and/or pre-existing blood dycrasias unless benefit outweighs risk. • Risk of folic acid deficiency • Oligospermia and infertility may occur in men treated with sulfasalazine (reversal within 2 to 3 months of stopping). • Risk of crystalluria – maintain adequate fluid intake. Important drug reactions: •azathioprine/mercaptopurine – increased bone marrow suppression •digoxin (decreased absorption) •Hypoglycaemic agents – increased hypoglycaemia
Pregnancy & Breastfeeding:	Refer to Section 9 (Guidance on use of DMARDS in pregnancy)
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/10722/SPC/Salazopyrin+En-Tabs/	

5. Biologic therapy (bDMARDs)

The use of bDMARDs is now relatively common in the management of a number of severe rheumatological conditions. Funding of biologic therapies falls outside of the national tariff. However where use is in accordance with NICE guidance local Clinical Commissioning Groups (CCG's) are automatically required to fund treatment. The reader should refer to the National Institute for Health and Care Excellence (NICE) website for details of NICE supported biologic treatment (http://www.nice.org.uk/.)

In addition to NICE, treatments may be commissioned nationally through the NHS Commissioning Board. Current NHS Board Commission Statements include the use of rituximab in the management of SLE and Behcets.

> Clinical Commissioning Policy: Rituximab for the treatment of Systemic Lupus Erythematosus (SLE), September 2013 ref: NHS England A13/PS/a (http://www.england.nhs.uk/wp-content/uploads/2013/09/a13-psa.pdf)

There are a number of conditions where there is an absence of NICE guidance or the patient is unable to fulfil the criteria of NICE or the NHS Commission Board. If biologic therapy is indicated, funding may be obtained through an individual funding request (IFR) or a locally agreed commissioning statement. The reader should refer to local hospital formulary and locally agreed treatment pathways/commissioning statements to clarify permitted prescribing practice.

There are currently five licensed Tumour Necrosis Factor (TNF) inhibitors in the UK: adalimumab, certolizumab pegol, etanercept, golimumab and infliximab of which 3 currently have available biosimilars (refer to Table 1). The reader should refer to individual product datasheets for more detailed prescribing guidance and also the NICE website with regards to funding status for use in different clinical indications. The attached monographs contain key information with regards to baseline and routine monitoring which should be performed with these agents.

In addition to the TNF inhibitors, the following licensed bDMARDs are available in the UK: abatacept, belimumab, tocilizumab, rituximab, ixekizumab, sarilumab, secukinumab, ustekinumab (please refer to Table 2). There are also 3 other targeted synthetic DMARDS currently available: tofacitinib, baricitinib and apremilast.

Table 1 Current licensed TNF inhibitors (TNFi) available in the UK

	Adalimumab (Humira®; Amgevita)	**Etanercept (Enbrel®; Benepali)**	**Certolizumab pegol (Cimzia®)**	**Golimumab (Simponi®)**	**Infliximab (Remicade®; Inflectra®; Remsima®; Flixabi®)**
Mechanism of action	Humanised monoclonal antibody	P75 fc fusion protein	Fab fragment	Humanised monoclonal antibody	Chimeric human/ murine antibody Intravenous infusion
Licensing indication	RA PsA AS nrAxial spondyloarthritis JIA	RA PsA AS nrAxial spondyloarthritis JIA	RA PsA and no response to other TNF inhibitors within 12 weeks AS nrAxial spondyloarthritis	RA + MTX only PsA +/- MTX AS	RA+MTX only PsA +/- MTX AS
NICE guidelines	RA: TA375; TA195 PsA: TA199 AS and nrAS: TA383	RA: TA375; TA195 PsA: TA199 AS and nrAS: TA383 JIA: TA373	RA: TA375; TA415 PsA: TA445 AS and nrAS: TA383	RA: TA375; TA225 PsA: TA220 AS: TA383 nrAS: TA497	RA: TA375; TA195 PsA: TA199 AS: TA383

Table 2 Non-TNF biologic medicines

Drug	**Abatacept (Orencia®)**	**Belimumab (Benlysta®)**	**Ixekizumab Taltz®)**	**Rituximab (Mabthera®)**	**Sarilumab (Kevzara®)**	**Secukinumab (Cosentyx®)**	**Tocilizumab (RoActemra®)**	**Ustekinumab (Stelara®)**
Mechanism of action	Fusion protein – blocks T cell activation	human, IgG1λ monoclonal antibody - blocks action of BLyS	IgG4 monoclonal antibody that binds 17A (both IL-17A and IL-17A/F)	Monoclonal antibody – CD20 B cell depletion	IgG1 subtype that specifically binds to both soluble and membrane-bound IL-6 receptors (IL-6Rα)	IgG1/κ monoclonal antibody that selectively binds to and neutralises IL-17A	Monoclonal antibody against soluble and membrane IL-6 receptor	IgG1κ monoclonal antibody that binds to the shared p40 protein subunit of IL-12 and IL-23
Licensing indication	Moderate to severe RA following DMARD failure (with MTX) JIA following failure of DMARD incl ≥1 TNFi	Add on therapy active autoantibody positive SLE with high disease activity (excluding CNS and lupus nephritis)	PsA, alone or in combination with MTX, when failed ≥2 DMARDS and ≥3 swollen + ≥ 3 tender joints OR no response to TNFs within 12 weeks OR TNF CI	RA (with MTX) following DMARD + TNFi failure ANCA associated vasculitis with glucocorticoids	RA +/-MTX following failure of DMARD	AS in patients who responded inadequately to NSAIDs or TNFi PsA (+/- MTX) when failed ≥2 DMARDS + ≥3 swollen + ≥ 3 tender joints OR no response to TNFs within 12 weeks OR TNF CI	RA (+/- MTX) following DMARD failure JIA (+/- MTX) GCA	PsA (+/- MTX) when ≥1 TNFi OR TNFi CI
NICE guidelines	RA: TA375; TA195 JIA: TA373	SLE: TA397	TA 537	RA: TA195 Vasculitis: TA308	TA485	AS: TA 407 PsA: TA445	RA: TA375; TA247 JIA: TA373 GCA: TA518	TA340

Table 3: targeted synthetic DMARDS

Drug	**Apremilast**	**Baricitinib**	**Tofacitinib**
Mechanism of action	PDE-4 inhibitor	Reversible JAK 1 and JAK 2 inhibitor	JAK inhibitor
Licensing indication	PsA	RA	RA PsA if TNFi CI or failed after 12 weeks
NICE guidelines	TA433	TA466	RA: TA480 PsA: TA543

Treatment with TNF inhibitors (safety issues)

Treatment for patients with active RA, PsA or AS where NICE approval exists.

For RA:

- Disease is severe, that is, a disease activity score (DAS28) greater than 5.1
- Disease has not responded to intensive therapy with a combination of csDMARDs

For PsA:

- The person has peripheral arthritis with 3 or more tender joints and 3 or more swollen joints
- The PsA has not responded to adequate trials of at least 2 csDMARDs, administered either individually or in combination.

In AS:

- Patients who have responded inadequately to, or who cannot tolerate, nonsteroidal anti-inflammatory drugs

To continue with biologics

For RA:

- At 6 months if there is a moderate response measured using EULAR criteria

For PsA:

- At 12 weeks (for certolizumab pegol also 16 weeks): an improvement in at least 2 of the 4 PsARC criteria (1 of which has to be joint tenderness or swelling score), with no worsening in any of the 4 criteria

For AS:

- At 12 weeks: a reduction in the BASDAI score to 50% of pre-treatment value or ≥2 units and
- A reduction in the spinal pain VAS score by ≥2 cm

1) General contraindications (discuss with relevant specialist)

Active infection

Open leg ulcers

Previously infected prosthetic joint (unless completely removed)

Septic arthritis in last year

HIV or Hepatitis B carriers (usually)

Previous malignancy within 5 years (usually)

NYHA Grade 3 or more heart failure

Any history of demyelinating disease

2) Relative contraindications

Uncontrolled diabetes

Pulmonary fibrosis

Bronchiectasis (assess severity)

PUVA therapy of >1000 Joules

Hepatitis C (absolute if RNA +ve)

NYHA heart failure grade 1 or 2

History of TB or positive PPD test (consider using rituxmab or isoniazid and pyridoxine one month before starting and for further 6 months)

3) Potential Problems

Atypical or unusual infections

Neutropenia / aplasia

Pneumonitis / lung fibrosis

Infusion / injection site reactions

ANA or DNA positivity (especially infliximab), although not usually associated with a clinical problem

Induction of autoimmunity

AVOID Live Vaccines (SEE VACCINES SECTION)

Abatacept (Orencia®)

Therapeutic class:	Fusion protein which moderates T lymphocyte-dependent antibody responses and inflammation (see p17)
Licensed Dose:	**RA (+methotrexate)** ● subcutaneous route - consider a single infusion loading dose followed by 125mg SC within a day and then 125mg SC weekly. ●IV infusion at week 0,2 and 4 then 4 weekly (<50kg give 500mg, 60 to 100kg give 750mg, >100kg give 1000mg).
Preparations:	250mg dry powder vial (administered by IV infusion in 100ml 0.9% sodium chloride over 30 minutes) and 125mg pre-filled syringe
NICE Guidance:	RA: TA375 and TA195 (after TNF failure if rituximab CI/failed) JIA: TA373
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	●Hypersensitivity to active substance or any excipient ●Severe and uncontrolled infections (sepsis/opportunistic) ●Avoid Live vaccines during and for 3 months after last dose.
Assessment of Response:	Clinical response should be carefully assessed, including DAS28 score at 3-6 months. Full clinical response may take longer to occur than with other biologic therapies.
Baseline Tests:	• Full clinical/infection screen • Urinalysis & BP • FBC/U&E/LFT/ANA/DNA • CXR (evidence TB/fibrosis) • Quantiferon or T-spot (as indicated) • Consider Hepatitis B&C + HIV • Pregnancy test if indicated
Routine Monitoring:	●Continue standard DMARD monitoring for methotrexate/other DMARDs the patient is taking ● If on monotherapy – FBC & LFT's at 1, 3 and 6 monthly
Indications for Stopping Therapy:	**Stop treatment if**: ●Evidence of active infection ●Pruritis/rash or symptoms suggestive of an allergic reaction Neutrophils < 1.6 x 10^{9}/L or below local normal range Platelets <140 x10^{9}/L or below local normal range AST or ALT > 3 times normal range (iu/L) **CONTACT THE RHEUMATOLOGY SERVICE**
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/27216/SPC/ORENCIA+125+mg+solution+for+injection+(pre-filled+syringe)/#INDICATIONS http://www.medicines.org.uk/EMC/medicine/19714/SPC/ORENCIA+250+mg+powder+for+concentrate+for+solution+for+infusion/	

Adalimumab (Humira®; Amgevita™)

Therapeutic Class:	Biologic - TNF Inhibitor
Licensed Indications:	Adalimumab is licensed for the following rheumatological conditions: • RA (with or without methotrexate, but combination preferred) • Polyarticular Juvenile Idiopathic Arthritis (with or without methotrexate, but combination preferred) • Ankylosing spondylitis • Psoriatic arthritis
Licensed Dose:	40 mg every other week as a single dose via subcutaneous injection (*The licensed datasheet states that RA patients receiving adalimumab monotherapy may benefit from once weekly administration.)
Preparations:	Pre-filled pen 40mg, prefilled syringe 40mg and single dose vial 40mg
NICE Guidance:	RA: TA375 and TA195 (after TNF failure if rituximab CI/failed) PsA: TA199 AS and nrAS: TA383 JIA: TA373
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	●Hypersensitivity to the active substance or to any of the excipients ●.Active tuberculosis or other severe infections such as sepsis, and opportunistic infections ●. Moderate to severe heart failure (NYHA class III/IV) * Patients treated with adalimumab should be given the special alert card.
Assessment of Response:	Full assessment of response at weeks 12 and 24, with treatment withdrawal if response is inadequate (reduction in DAS28<1.2 or overall DAS28>3.2). If response to treatment is not maintained, a repeat assessment should occur.
Baseline Tests:	• Full clinical/infection screen • Urinalysis & BP • FBC/U&E/LFT/ANA/DNA • CXR (evidence TB/fibrosis) • Quantiferon or T-spot when indicated • Hepatitis B and C + consider HIV • Pregnancy test if indicated (although considered safe for conception)
Routine Monitoring:	• Usual tests for methotrexate or other DMARD • If monotherapy FBC/LFTs at 1,3 and 6 months, then 6 monthly • Consider checking pre-dose drug levels and anti-drug antibody levels especially if secondary non-response clinically
Indications for Stopping Therapy:	**Stop if:** ●Evidence of infection ●Possible demyelination ●SLE / new autoimmune syndrome ●Severe injection site reaction (If minor reaction try oral anti-histamine or topical corticosteroids) ●Rash - caution very rarely Steven Johnsons Syndrome Neutrophils < 1.6 x 10^{9}/L or below local normal range Platelets <140 x10^{9}/L or below local normal range AST or ALT > 3 times normal range (iu/L) **CONTACT THE RHEUMATOLOGY SERVICE**
Please refer to licensed datasheet for more comprehensive prescribing information: https://www.medicines.org.uk/emc/product/2150/smpc	

Belimumab (Benlysta®)

Therapeutic class:	Belimumab is a human, IgG1λ monoclonal antibody - blocks action of BLyS (B Lymphocyte Stimulator Protein)
Licensed Indications:	Add on therapy in adult patients with active, autoantibody positive SLE with a high degree of disease activity despite standard therapy (usually in a tertiary centre setting)
Licensed Dose:	10 mg/kg on Days 0, 14 and 28, and at 4-week intervals thereafter.
Preparation:	120mg vial (80mg/ml) & 400mg vial (80mg/ml) - in 250ml 0.9% sodium chloride or 5% glucose over 60 minutes.
NICE Guidance:	SLE: TA397
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	●Live vaccines must not be given during or 30 days before commencing treatment ● Hypersensitivity to the active substance or to any of the excipients ●Chronic or severe or opportunistic infections (risk in active or latent TB unknown) ● Malignant neoplasm within last 5 years. ●Acute hypersensitivity reactions reported to occur several hours after completion and even the day after infusion. ●Has not been studied in combination with cyclophosphamide or other B cell targeted therapies.
Pregnancy & Breastfeeding:	Please contact the Rheumatologist if patient considering conceiving or in case of pregnancy. • Females to use effective contraception during treatment and for 4 months after stopping (*datasheet states do not use during pregnancy unless clearly necessary). • Breastfeeding - risk unknown (Contact the Hospital Pharmacy Medicines Information Department)
Assessment of Response:	Discontinuation of treatment should be considered if there is no improvement in disease control after 6 months of treatment.
Baseline Tests:	• Full clinical/infection screen • Urinalysis & BP • FBC/U&E/LFT/ANA/DNA • B Cell analysis • Immunoglobulins • CXR • Consider Hepatitis B&C, HIV • Pregnancy test if indicated • Consider TB screening (not done routinely)

Routine Monitoring:	●Continue routine DMARD monitoring for concomitant therapies. ●exclude presence of infection prior to each infusion ●Urinalysis before each infusion ●FBC/U&E's before each infusion ●BP prior to infusion, 30 minutes after the start, at the end of the infusion and 30 minutes post
Indications for Stopping Therapy:	**Stop treatment if:** ●Evidence of active infection ●Hypersensitivity reaction ● Neut < 1.6 10^{9}/L ●Increased insomnia/change in mood **CONTACT THE RHEUMATOLOGY SERVICE**
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/24769/SPC/Benlysta+120+mg+and+400+mg+powder+for+concentrate+for+solution+for+infusion/	

Certolizumab Pegol (Cimzia®)

Therapeutic Class:	Biologic - TNF α Inhibitor
Licensed Indications:	RA in combination with methotrexate (datasheet permits use without methotrexate where there is intolerance), PsA, AS Licensed for use in both breastfeeding and pregnancy and may be considered treatment of choice in this situation
Licensed Dose:	400 mg (as two s/c injections of 200 mg each on one day) at weeks 0, 2 and 4, followed by a maintenance dose of 200 mg every 2 weeks Missed dose: Patients who miss a dose should be advised to inject the next dose as soon as they remember and then continue injecting subsequent doses every 2 weeks as originally instructed
Preparations:	200mg prefilled syringe
NICE Guidance:	RA: TA375 and TA415 (after TNF failure if rituximab CI/failed) PsA: TA445 AS and nrAS: TA383
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	● Live vaccines must not be given● Hypersensitivity to the active substance or to any of the excipients ● Active tuberculosis (TB) or other severe infections such as sepsis, and opportunistic infections ● Moderate or severe heart failure (NYHA class III/IV) *The datasheet contains a warning regarding a minor influence on the ability to drive and use machines, (including vertigo, vision disorder and fatigue) may occur following administration
Assessment of Response:	Available data suggest that clinical response is usually achieved within 12 weeks of treatment (refer to BSR/NICE guidance regarding definition of "adequate response").
Baseline Tests:	• Full clinical/infection screen • Urinalysis & BP • FBC/U&E/LFT/ANA/DNA • CXR (evidence TB/fibrosis) • Quantiferon or T-spot (as indicated) • Hepatitis B and C + consider HIV
Routine Monitoring:	Continue standard DMARD monitoring, if monotherapy FBC/LFT at 1, 3 and 6 months and then 6 monthly
Indications for Stopping Therapy:	**Stop if:** ●Evidence of infection ●Possible demyelination ●SLE or new autoimmune syndrome ●Severe injection site reaction (If minor reaction try oral/topical anti-histamine or topical corticosteroids) Neutrophils < 1.6 x $10^{9/}$L or below local normal range Platelets <140 x$10^{9/}$L or below local normal range AST or ALT > 3 times normal range (iu/L) **CONTACT THE RHEUMATOLOGY SERVICE**
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/22323/SPC/Cimzia+200+mg+solution+for+injection/	

Etanercept (Enbrel®; Benepali®)

Therapeutic Class:	Biologic - TNFα Inhibitor
Licensed Indications:	Etanercept is licensed for the following rheumatological conditions: • RA (with or without methotrexate, but combination preferred) • JIA (with or without methotrexate, but combination preferred) • AS • PsA
Licensed Dose:	50mg weekly or 25mg twice a week by subcutaneous injection
Preparations:	50mg & 25mg prefilled syringe, 50mg prefilled pen, 25mg & 10mg dry powder vial.
NICE Guidance:	RA: TA375 and TA195 (after TNF failure if rituximab CI/failed) PsA: TA199 AS and nrAS: TA383 JIA: TA373
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	● Live vaccines must not be given● Hypersensitivity to the active substance or to any of the excipient (needle cover of prefilled syringe contains latex) ● Active tuberculosis** (TB) or other severe infections such as sepsis, and opportunistic infections ● Caution in patients with congestive cardiac failure. *Patients treated with etanercept should be given the Patient Alert Card. **May be preferred TNFi where previous TB contact but no active infection.
Assessment of Response:	Full assessment of response at weeks 12 and 24, with treatment withdrawal if response is inadequate (reduction in DAS28<1.2 or overall DAS28>3.2). If response to treatment is not maintained, a repeat assessment should occur.
Baseline Tests:	• Full clinical/infection screen • Urinalysis & BP • FBC/U&E/LFT/ANA/DNA • CXR (evidence TB/fibrosis) • Quantiferon or T-spot (as indicated) • Hepatitis B and C + consider HIV • Pregnancy test if indicated (although considered safe for conception)
Routine Monitoring:	Continue standard DMARD monitoring. If monotherapy FBC/LFT at 1, 3 and 6 months then 6 monthly
Indications for Stopping Therapy:	**Stop if:** ●Evidence of infection ●Possible demyelination ●SLE or other autoimmune syndrome ●Severe injection site reaction (If minor reaction try oral anti-histamine or topical corticosteroids) Neutrophils < 1.6 x $10^{9/}$L or below local normal range Platelets <140 x$10^{9/}$L or below local normal range AST or ALT > 3 times normal range (iu/L) **CONTACT THE RHEUMATOLOGY SERVICE**
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/19162/SPC/Enbrel+50mg+solution+for+injection+in+pre-filled+syringe/ https://www.medicines.org.uk/emc/product/1987/smpc	

Golimumab (Simponi®)

Therapeutic Class:	Biologic - TNF Inhibitor (Human monoclonal antibody)
Licensed Indications:	RA (in combination with methotrexate), PsA & AS
Licensed Dose:	RA, PsA & AS - 50 mg given once a month by sc injection, on the same date each month. Increased dose: Patients weighing more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses of 50mg, should have their dose increased to 100 mg once a month. Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg. Missed dose: if the dose is less than 2 weeks late, the patient should inject his/her forgotten dose and stay on his/her original monthly schedule. If the delay is more than 2 weeks a new monthly schedule should be established.
Licensed preparation:	Prefilled pen and prefilled syringe in 50mg and 100mg strength
NICE Guidance:	RA: TA375; TA225 (after TNF failure if rituximab CI/failed) PsA: TA220 AS: TA383 nrAS: TA497
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	● Live vaccines must not be given● Hypersensitivity to the active substance or to any of the excipients - including latex sensitivity (golimumab pen) ● Active tuberculosis (TB) or other severe infections such as sepsis, and opportunistic infections ● Moderate or severe heart failure (NYHA class III/IV) ● Contains Sorbitol - not in hereditary problems with fructose intolerance.
Assessment of Response:	Available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses) - see information on increased dose plus BSR/NICE guidance regarding adequate response.
Baseline Tests:	• Full clinical/infection screen • Urinalysis & BP • FBC/U&E/LFT/ANA/DNA • CXR (evidence TB/fibrosis) • Quantiferon or T-spot (as indicated) • Hepatitis B and C + consider HIV • Pregnancy test if indicated (though considered safe for conception)
Routine Monitoring:	Continue standard DMARD monitoring, if monotherapy FBC/LFT at 1, 3 and 6 months then 6 monthly
Indications for Stopping Therapy:	**Stop if:** ●Evidence of infection ●Possible demyelination ●SLE / autoimmune syndrome ●Severe injection site reaction (If minor reaction try oral anti-histamine or topical corticosteroids) Neutrophils < 1.6 x 10^{9}/L or below local normal range Platelets <140 x10^{9}/L or below local normal range AST or ALT > 3 times normal range (iu/L) **CONTACT THE RHEUMATOLOGY SERVICE**
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/23766/SPC/Simponi+50+mg+solution+for+injection/	

Infliximab (Remicade®; Inflectra®; Remsima®; Flixabi®)

Therapeutic Class:	Biologic - TNF □ Inhibitor (chimeric human-murine IgG1 monoclonal antibody)
Licensed Indications:	RA (in combination with methotrexate);AS;PsA
Licensed Dose:	**RA** - 3mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter (refer to datasheet regarding non-standard increased doses and reduced dosage intervals in RA). For disease that has an inadequate response or loss of response after 12 weeks of treatment, consideration may be given to increasing the dose step-wise by approximately 1.5 mg/kg up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg as often as every 4 weeks may be considered. **AS** -5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. **PsA** - 5mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Dosing may be informed by measuring pre-treatment levels
Preparations:	100 mg powder vial (Administered in 250ml 0.9% sodium chloride, first 3 infusions over 2 hours, infusion 4 to 10 over 60 minutes thereafter over 30 minutes).
NICE Guidance:	RA: TA375 and TA195 (after TNF failure if rituximab CI/failed) PsA: TA199 AS: TA383
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	● Live vaccines must not be given ●Hypersensitivity to the active substance or to any of the excipients (including other murine proteins) ●.Active tuberculosis or other severe infections such as sepsis, and opportunistic infections ●. Moderate to severe heart failure (NYHA class III/IV) *Patients treated with infliximab should be given the package leaflet and the special Alert card. Infusion reactions may be increased when combined with leflunomide
Pregnancy & Breastfeeding:	Please contact the Rheumatologist if patient considering conceiving or in case of pregnancy. (*Administration of live vaccines to infants exposed to infliximab in utero is not recommended for 6 months following the mother's last infliximab infusion during pregnancy)
Assessment of Response:	Full assessment of response at weeks 12 and 24, with treatment withdrawal if response is inadequate (reduction in DAS28<1.2 or overall DAS28>3.2). If response to treatment is not maintained, a repeat assessment should occur (refer to BSR/NICE guidance regarding adequate response).
Baseline Tests:	• Full clinical/infection screen • Urinalysis & BP • FBC/U&E/LFT/ANA/DNA • CXR (evidence TB/fibrosis) • Quantiferon or T-spot (as indicated) • Hepatitis B&C + consider HIV • Pregnancy test if indicated (though considered safe for conception)

Routine Monitoring:	Continue standard DMARD monitoring FBC/LFT/U&E or 2 monthly (before each infusion) + Urinalysis before each infusion Consider measuring drug levels especially if evidence of secondary non response
Indications for Stopping Therapy:	**Stop if:** ●Evidence of infection ●Possible demyelination ●SLE or other autoimmune syndrome ●Severe injection site reaction (If minor reaction try oral anti-histamine or topical corticosteroids) Neutrophils < 1.6 x $10^{9/}$L or below local normal range Platelets <140 x$10^{9/}$L or below local normal range AST or ALT > 3 times normal range (iu/L) **CONTACT THE RHEUMATOLOGY SERVICE**
Please refer to licensed datasheet for more comprehensive prescribing information: https://www.medicines.org.uk/emc/product/3831/smpc https://www.medicines.org.uk/emc/product/3710/smpc https://www.medicines.org.uk/emc/product/7265/smpc https://www.medicines.org.uk/emc/product/3709/smpc	

Ixekizumab (Taltz®)

Therapeutic class:	IgG4 monoclonal antibody that binds 17A (both IL-17A and IL-17A/F)
Licensed Dose:	**PsA** - 160mg sc week 0,then 80mg every 4 weeks with or without MTX
NICE Guidance:	TA 537
Renal/hepatic impairment	Not studied - no dose recommendation can be made
Elderly	No dose adjustment
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	Do not give in active TB Increased risk infection - URTI, candidiasis and conjunctivitis Caution if history of chronic infection Risk hypersensitivity reactions (can be 10-14 days post injection) May cause or exacerbate Crohn's and ulcerative colitis May cause neutropenia and/or thrombocytopenia Manufacturer advises avoid with live vaccines
Pregnancy & Breastfeeding:	No data available. Manufacturer advises women of childbearing potential - contraception during and for at least 10 weeks after treatment. Breastfeeding - not recommended
Assessment of Response:	NICE - PsARC 16 wk, 2 out of 4 including joint tenderness and swelling
Baseline Tests:	FBC LFT's U&E Consider CXR Consider Hepatitis B and C, Quantiferon or T-spot, and HIV testing Consider Urinalysis *Consider pregnancy test
Routine Monitoring:	FBC is recommended 6 monthly or if symptomatic
Indications for Stopping Therapy:	ANC <1.0 x 10^9cells/L Platelets 50-100 x 10^9cells/L Serious infection Or chronic infection not responding to standard treatment Suspected hypersensitivity reaction (injection site rash, rash, urticaria, dyspnoea) Worsening of Crohn's/UC.
Please refer to licensed datasheet for more comprehensive prescribing information: https://www.medicines.org.uk/emc/product/7233/smpc	

Rituximab (Mabthera®; Truxima®)

Therapeutic class:	Rituximab - chimeric mouse/human monoclonal antibody, binds to transmembrane antigen CD20 resulting in B cell lysis
Licensed Indications:	**RA** - (with methotrexate) adult patients with severe active RA who have had an inadequate response or intolerance to other DMARD's, including one or more tumour necrosis factor (TNF) inhibitor therapies.(*Used off license as monotherapy or in combination with an alternative DMARD or without prior treatment with a TNF inhibitor for RA) **CTD** - used for a number of autoimmune disorders including SLE, Vasculitis, Antiphospholipid Syndrome, Myositis and Scleritis. (Holds a licence for Granulomatosis with polyangiitis (GPA) and Microscopic polyangiitis (MPA). If used in CTD consider the need for oral steroids between the first and second infusion e.g. prednisolone 30mg od 2 weeks. Patients receiving Rituximab under NHS Clinical Commissioning Policies should be enrolled in a regional or national database.
Licensed Dose:	**RA** - 1g iv infusion followed by a second 1g iv infusion two weeks later. Pre-treatment with methylprednisolone 100mg 30 minutes prior to infusion plus paracetamol and an anti-histamine recommended (*also a reduce dosage regime - two doses of 500mg two weeks apart in patients who have received repeated cycles and have achieved adequate clinical response and B cell depletion). **GPA and MPA** - 375 mg/m2 body surface area, once weekly iv infusion for 4 weeks (four infusions in total – though some specialists use the RA protocol). Consider IV Methylprednisolone for 1 to 3 days at a dose of 250-500mg per day prior to the first infusion of rituximab. This should be followed by oral prednisone 1 mg/kg/day (not to exceed 80mg/day, and tapered as rapidly as possible based on clinical need) during and after rituximab treatment. (*PCP prophylaxis is recommended for patients with GPA or MPA). RA dosing has also been widely used to treat AAV and CTD's. **Repeat Dosing** – Usually this is done on the basis of clinical relapse in RA and CTD, but in some areas has been at fixed 6 monthly cycles (notably in AAV). RA non-responders (especially when non depleted) may respond to retreatment at 6 months.
Infusion details:	1g dose infused in 250ml 0.9% sodium chloride, 1st infusion start at 50mg/hr increasing at 50mg/hr increments every 30 minutes to a maximum of 400mg/hr, 2nd infusion initial rate 100mg/hr increasing at 100mg/hr increments every 30 minutes up to a maximum of 400mg/hr). Where RA patients have had no prior reactions an accelerated 2 hour infusional regimen can be employed (refer to current product SPC)
NICE Guidance/NHS Commission:	RA: TA195 Vasculitis: TA308 SLE: Clinical Commissioning Policy: Rituximab for the treatment of Systemic Lupus Erythematosus (SLE), September 2013: NHS England

Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	●Hypersensitivity to the active substance/excipients (incl. murine proteins) ●Severe heart failure (NYHA IV) or severe, uncontrolled cardiac disease ●Active, severe infections● Severely immunocompromised
Assessment of Response:	Review 16-20 weeks after each cycle. Not all patients achieve adequate B cell depletion after the first cycle. (Inadequate depletion after cycle 1 = consider a repeat cycle at 3-6 months if available). Leeds HMDS B cell subsets at day 15 predict response in RA and at 6 weeks in SLE. Equally subsets at 6 months can help predict relapse in SLE and AAV.
Baseline Tests:	Full clinical/infection screen - CXR, urinalysis, hepatitis B&C, consider HIV and TB screening. FBC/U&E/LFT B Cell FACS analysis & Immunoglobulins (when IgG <6g/l increased risk of serious infections) Pregnancy test if indicated
Routine Monitoring:	If receiving csDMARD continue routine monitoring for concomitant therapy. Before first infusion of each cycle ●Urinalysis ●BP ●FBC/U&E's For repeat cycles of rituximab: ●Clinical review ●Immunoglobulins HMDS subsets at 0, day 15, 6 weeks and 3 monthly can help with planning management (as above)
Indications for Stopping Therapy:	**Stop if** :●Neurological/cognitive/psychiatric symptoms – refer immediately to Rheumatology Service (very rarely PML) ● Facial flushing and sore throat are common minor infusion reactions which often occur during infusion, but may occur 24-48 hours after treatment ● If significant infusion reaction occurs stop infusion, administer IV antihistamine and restart as per protocol. More severe or persistent infusion reactions may require discontinuation. Prolonged reactions with flu like symptoms, headache, vasculitic rash and low complement may indicate immunogenicity. This is most common in CTD and may respond to prophylactic corticosteroids ● Significant rash or any evidence of infection occurs stop treatment ● Sore throat/ulceration can be a late complication related to neutropenia (6/52 – 6/12) so check FBC. ● Immunoglobulin IgG level <6g/l – consider discussion with Leeds Service ● **If unsure contact local rheumatology service.**
Please refer to licensed datasheet for more comprehensive prescribing information: https://www.medicines.org.uk/emc/product/3801/smpc https://www.medicines.org.uk/emc/product/8878/smpc	

Sarilumab (Kevzara®)

Therapeutic class:	IgG1 subtype that specifically binds to both soluble and membrane-bound IL-6 receptors (IL-6Rα)
Licensed Dose:	**RA** - 200mg sc once every 2 weeks (with/without mtx). 150 mg once every 2 weeks is recommended for management if neutropenia, thrombocytopenia, or liver enzyme elevations.
NICE Guidance:	TTA485
Renal/hepatic impairment/Elderly	No dose adjustment
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	Risk of hypersensitivity reaction - counsel patients Not in active infection (incl. localised) Serious infection risk (bacterial, fungal, viral & opportunistic) - caution chronic/recurrent infection hx. Risk colonic perforation (caution diverticulitis) - promptly evaluate abdominal symptoms Is associated with low ANC and/or platelets plus abnormal LFT's – use contraindicated if ANC <2.0 x 10^9cells/L, Platelets < 150 x 10^9cells/L, initiating AST/ALT 1.5 X ULN or halting at x5 ULN) Manufacturer advises avoid with live vaccines
Pregnancy & Breastfeeding:	No data available but manufacturer recommends women of childbearing potential - contraception during and up to 3 months after treatment (if pregnancy occurs - evaluate clinical need to continue). Breastfeeding not recommended.
Assessment of Response:	NICE - moderate EULAR response at 6 months
Baseline Tests:	FBC, U&E, LFTs Consider CXR Consider Hepatitis B and C, Quantiferon or T-spot (if appropriate), and HIV testing Consider Urinalysis *Consider pregnancy test
Routine Monitoring:	FBC and LFT's - at 4 to 8 weeks then suggest 3 monthly Lipids - at 4 to 8 weeks then 6 monthly (***Take bloods at the end of the dosing interval when considering dose modification)**
Indications for Stopping Therapy:	ANC <1.0 x 10^9cells/L Platelets <50 x 10^9cells/L LFT's 3 to 5 x ULN (Treatment with Kevzara should be withheld until < 3 x ULN then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate; treatment with Kevzara should be discontinued if ALT > 5 x ULN) Serious infection/Opportunistic infection New onset abdominal symptoms Suspected Hypersensitivity reaction - Injection site rash, rash, urticaria
Please refer to licensed datasheet for more comprehensive prescribing information: https://www.medicines.org.uk/emc/product/8143/smpc	

Secukinumab (Cosentyx®)

Therapeutic class:	IgG1/κ monoclonal antibody that selectively binds to and neutralises IL-17A
Licensed Dose:	**PsA** - concomitant psoriasis or TNFi inadequate responder 300mg sc wk 0,1,2,3 and 4 the monthly. Otherwise 150mg wk 0,1,2,3 and 4 then monthly **AS** - 150mg sc wk 0,1,2,3 and 4 then monthly
NICE Guidance:	AS: TA 407 PsA: TA445
Renal/hepatic impairment/Elderly	No dose adjustment
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	C/I Severe, active infection Caution chronic or recurrent infection or persistent candidiasis Active Crohn's disease - risk of exacerbation Latex allergy - risk of reaction due to needle cap Risk of neutropenia Risk of hypersensitivity reaction
Pregnancy & Breastfeeding:	Women of childbearing potential - contraception during and for at least 20 wks after treatment. Breastfeeding - not recommended
Assessment of Response:	PsA- PsARC 24 wk, 2 out of 4 incl joint tenderness or swelling, plus no worsening of criteria AS- 16 wk BASDAI 50% reduction or at least 2 units plus at least 2cm improvement in VAS
Baseline Tests:	FBC LFT's U&E Consider CXR Consider Hepatitis B and C, Quantiferon or T-spot (if appropriate), and HIV testing Consider Urinalysis Consider pregnancy test
Routine Monitoring:	Current advice is FBC and LFTs 6 monthly, but this is not mandated
Indications for Stopping Therapy:	Severe infection Exacerbation of Crohn's ANC <1.0 *10^9 cell/L Symptoms suggestive of hypersensitivity - injection site rash, rash, urticaria and/or dyspnoea
Please refer to licensed datasheet for more comprehensive prescribing information: https://www.medicines.org.uk/emc/product/3669/smpc	

Tocilizumab (Roactemra®)

Therapeutic Class:	Biologic - humanised IgG1 monoclonal antibody against the human interleukin-6 (IL-6) receptor (see p17)
Licensed Indications:	**RA** (with or without MTX), **JIA, GCA**
Licensed Dose:	**RA - intravenous infusion** 8 mg/kg body weight, given once every four weeks (maximum recommended dose 800mg) **subcutaneous injection -** 162mg once every week. **sJIA** -8 mg/kg once every 2 weeks in patients weighing greater than or equal to 30 kg or 12 mg/kg once every 2 weeks in patients weighing less than 30 kg (For the unlicensed indication of AOSD use the same dose as recommended for sJIA). Refer to datasheet for dosage adjustment or interruption when abnormal LFT's, neutrophils or platelets.
Preparation:	• Vial 80 mg, 200mg & 400 mg (all 20 mg/ml), Given as an intravenous infusion in 100ml 0.9% sodium chloride over 60 minutes. • 162 mg solution for injection in pre-filled syringe
NICE Guidance:	RA: TA375 and TA247 (after TNF failure if rituximab CI/failed) JIA: TA373 In combination with methotrexate - after TNFi failure and rituximab CI or following rituximab treatment failure (TA247) JIA: TA373 GCA: TA518
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	● Live and attenuated live vaccines must not be given ● Hypersensitivity to the active substance or to any of the excipients ● Active tuberculosis (TB) or other severe infections such as sepsis, and opportunistic infections ● Active hepatic disease or impairment ● Pre-existing neutropenia ●Gastro-intestinal ulcers or Diverticulitis ●Interstitial lung disease (increased risk of infection; reports of developing pneumonitis and fibrosis) ● **Drug interactions:** statins (simva, atorva, lora), calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin, or benzodiazepines - dose increases may be required to maintain therapeutic effect of these medicines. *All patients treated with RoActemra should be given the Patient Alert Card.
Assessment of Response:	Available data suggest that clinical improvement is observed within 6 weeks of initiation of treatment with tocilizumab (refer to BSR/NICE guidance regarding adequate response).
Baseline Tests:	• Full clinical/infection screen • Urinalysis & BP • FBC/U&E/LFT/ANA/DNA (contraindicated if LFT's > 5*ULN or absolute neutrophil count <1.0 x 10^9 /l) • CXR (evidence TB/fibrosis) • Consider Hepatitis B and C, Quantiferon or T-spot (if appropriate), and HIV testing • Baseline lipids • Pregnancy test if indicated
Routine Monitoring:	As for DMARD therapy or ● LFT's (Transaminases), neutrophils and platelets 3 monthly ● Lipid parameters - assessment of lipid parameters at 3 months only. If infusion only, bloods prior to each infusion.
Indications for Stopping Therapy:	**Stop if**: ●*Infusion reaction ● Evidence of infection ●Development of new abdominal symptoms ●Deterioration in lung function (perform CXR / PFT) ● LFT's transaminases persistently > 3 xULN ● Neutrophils < 1.0 x10^9 /l ● Platelets < 100 x10^9 ● Macrophage activation syndrome (MAS) reported in sJIA *Mild infusion reaction common within 24 hours of the first infusion. Severe reaction may be observed between 2nd to 5th infusion
Please refer to licensed datasheet for more comprehensive prescribing information: https://www.medicines.org.uk/emc/product/6673/smpc https://www.medicines.org.uk/emc/product/5357/smpc https://www.nice.org.uk/guidance/TA518	

Ustekinumab (Stelara®)

Therapeutic class:	IgG1κ monoclonal antibody that binds to the shared p40 protein subunit of IL-12 and IL-23
Licensed Dose:	**PsA** - 45mg sc then 45mg 4 weeks later and then 45mg 12 weekly. Consider 90mg dose if >100kg
NICE Guidance:	TA340
Renal/hepatic impairment/Elderly	No dose adjustment
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	Caution in active or chronic infection Caution if history of malignancy Latex allergy - avoid pre-filled syringe Risk of hypersensitivity reaction
Pregnancy & Breastfeeding:	No data but manufacturer advises women of childbearing potential - contraception during and for at least 15 wks after treatment. Breastfeeding - not recommended
Assessment of Response:	PsA- PsARC 24 wk, 2 out of 4 incl joint tenderness or swelling, plus no worsening of criteria
Baseline Tests:	FBC LFT's U&E Consider CXR Consider Hepatitis B and C, Quantiferon or T-spot (if appropriate), and HIV testing Consider Urinalysis *Consider pregnancy test
Routine Monitoring:	FBCs if symptoms of infection > 60 yrs - skin checks for non-melanoma skin cancer Monitor for symptoms of erythrodermic psoriasis or exfoliative dermatitis
Indications for Stopping Therapy:	Active infection Symptoms of erythrodermic psoriasis or exfoliative dermatitis Symptoms suggestive of hypersensitivity - injection site rash, rash, urticaria and/or dyspnoea
Please refer to licensed datasheet for more comprehensive prescribing information: https://www.medicines.org.uk/emc/product/4412/smpc	

6. Targeted Synthetic DMARDS (tsDMARDS)

Apremilast (Otezla®)

Therapeutic class:	PDE-4 inhibitor
Licensed Dose:	**PsA** - Day 1 10mg od, Day 2 10mg bd, Day 3 10mg om + 20mg on, Day 4 20mg bd, Day 5 20mg om + 30mg on then Day 6+ 30mg bd and continue
NICE Guidance:	TA433
Renal Impairment	Dose adjustment only when CrCl < 30ml/min - titrate using morning dose only to max 30mg od
Hepatic impairment/elderly	No dose adjustment required (higher risk GI effects in elderly)
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	GI side effects common in first 2- 4 weeks Use associated with insomnia and depression - caution in patients prior hx, counsel re reporting suicidal ideation/mood change Contains lactose - avoid in Lapp lactase deficiency or glucose-galactose malabsorption
Pregnancy & Breastfeeding:	No data but manufacturer recommends women of childbearing potential should use an effective method of contraception to prevent pregnancy during treatment. Contraindicated in pregnancy and breast-feeding
Assessment of Response:	PsA- PsARC 24 wk, 2 out of 4 incl joint tenderness or swelling, plus no worsening of criteria
Baseline Tests:	Body weight Consider history of psychiatric/depression *Consider pregnancy test
Routine Monitoring:	Monitor for weight loss - weight check each clinic visit - discontinuation of treatment should be considered in unexplained and clinically significant weight loss Changes in mood
Indications for Stopping Therapy:	Severe diarrhoea, nausea, or vomiting - discontinue Significant weight loss in patients especially if pre-existing low BMI Change in mood/suicidal thoughts/insomnia
Please refer to licensed datasheet for more comprehensive prescribing information: https://www.medicines.org.uk/emc/product/3649	

Baricitinib (Olumiant®)

Therapeutic class:	Reversible JAK 1 and JAK 2 inhibitor
Licensed Dose:	**Moderate to Severe RA** - 4mg od with or without mtx (↓2mg od chronic/recurrent infection/≥ 75 years)
NICE Guidance:	TA466
Renal Impairment	CrCl 30-60ml/min 2mg od CrCl <30ml/min do **not** use
Hepatic Impairment	Mild/mod - no dose ↓ Severe - do not use in severe cirrhosis (Childs Pugh C)
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	Contraindication absolute lymphocytes count <0.5 x 10^9cells/L, ANC <1.0 x 10^9cells/L, Hb <8g/dL Risk DVT/PE - use with caution in high risk individuals (older age, obesity, PMH DE/PVT, surgery and immobile) Risk of herpes virus reactivation
Pregnancy & Breastfeeding:	Manufacturer advises women of child-bearing potential to use contraception during treatment and at least 1 week after stopping. Avoid in pregnancy and breast-feeding
Assessment of Response:	NICE - moderate EULAR response at 6 months
Baseline Tests:	FBC, U&E, LFT's Quantiferon or T-spot if appropriate Hepatitis B and C (patients with active hepatitis B or C infection were excluded from clinical trials. Monitor for expression of Hep B virus DNA – consult hepatologist)/HIV Lipids Risk of herpes zoster re-activation. Consider herpes Zoster vaccine in patients at least 2 weeks, ideally 4 weeks, before starting this DMARD Consider pregnancy test
Routine Monitoring:	As per concurrent DMARD. If monotherapy: FBC, U&Es, LFTs every 2 weeks until on stable dose for 6 weeks Once on stable dose, monthly for 3 months and then 6 monthly Check lipids 8-12 weeks after commencement - treat according to current guidance and monitor accordingly CK levels may be elevated – the clinical significance of this is unknown
Indications for Stopping Therapy:	Hb <8g/dL ALC <0.5 x 10^9 cells/L ANC <1.0 x 10^9 cells/L ALT/AST > x3 ULN CrCl <30ml/min Suspected DVT/PE Herpes Zoster/Simplex infection Active infection not responding to standard treatment Pregnancy
Please refer to licensed datasheet for more comprehensive prescribing information: https://www.medicines.org.uk/emc/product/2434	

Tofacitinib Citrate (Xeljanz®)

Therapeutic class:	JAK inhibitor
Licensed Dose:	**Moderate to severe RA** - 5mg bd with or without MTX PsA – 5mg BD
NICE Guidance:	RA: TA480 PsA: TA543
Renal Impairment	Dose adjustment only when CrCl <30ml/min: max dose 5mg od
Hepatic Impairment	Avoid in patients with cirrhosis
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	C/I ALC <0.75 x 10^9cells/L, ANC <1.0 x 10^9cells/L, Hb <9g/dL Gastrointestinal perforation – possible increased risk. Use with caution in those with increased risk (e.g. diverticulosis); promptly evaluate abdominal symptoms Interstitial lung disease – possible increased risk Malignancy risk uncertain Reactivation of herpes virus Contains lactose - avoid in Lapp lactase deficiency or glucose-galactose malabsorption
Pregnancy & Breastfeeding:	No data. Manufacturer recommends women of child-bearing potential to use contraception during treatment and at least 4 weeks after stopping. Avoid in pregnancy and breast-feeding
Assessment of Response:	NICE - moderate EULAR response at 6 months
Baseline Tests:	FBC, U&Es, LFTs Lipids Consider CXR Consider Hepatitis B and C, quantiferon (or T-spot if appropriate), HIV testing Consider Urinalysis Risk of herpes zoster re-activation. Consider herpes Zoster vaccine in patients at least 2 weeks, ideally 4 weeks, before starting DMARD *Consider pregnancy test FBC
Routine Monitoring:	As per concurrent DMARD. If monotherapy: FBC, U&Es, LFTs every 2 weeks until on stable dose for 6 weeks Once on stable dose, monthly for 3 months and then 6 monthly Lipids - at 8-12 weeks, treat according to current guidance Periodic skin examination (risk non-melanoma skin cancer)
Indications for Stopping Therapy:	Absolute lymphocyte count - 2 sequential routine monitoring values between 0.5 and 0.75 x 10^9 cells/L , stop and restart when >0.75 x 10^9 cells/L . If value <0.5 x 10^9 cells/L repeat test within 7 days and stop if still <0.5 ANC - 2 sequential routine monitoring values between 0.5 and 1.0 x 10^9cells/L , stop and restart when >1.0. If value <0.5 x 10^9cells/L repeat test within 7 days and stop if still <0.5. Hb - >2g/dL decrease or <8.0g/dL, stop and await normalisation of Hb Serious infection Pregnancy Abdominal symptoms suggesting perforation,
Please refer to licensed datasheet for more comprehensive prescribing information: https://www.medicines.org.uk/emc/product/2500/smpc	

7. Guidance on vaccination and travel in patients receiving DMARDs

Live vaccines can cause severe or fatal infections in immunocompromised individuals. If a live vaccination is required it should be performed at least 2, and ideally 4 weeks, prior to starting treatment with most synthetic and all bDMARDs. It should be given at least 3 weeks before immunoglobulins.

Vaccination status should be evaluated before commencing treatment with most DMARDs (except HCQ, SSA and Gold), and especially bDMARDs.

Patients on stable long term low dose corticosteroid therapy (defined as up to 20mg prednisolone per day for more than 14 days in adult) either alone or in combination with low dose non-biological oral immune modulating drugs (e.g. methotrexate 25mg per week in adult or azathioprine 3.0mg/ kg/day) can receive live vaccines. In the case of yellow fever vaccine data is limited, and a cautious approach is recommended

Patients >50 years should undergo vaccination against herpes zoster assuming there are no contraindications. Zostavax is currently licensed and recommended in rheumatology patients over age 50 years. It is a live vaccine and it should be given to patients with a **history** of chicken pox (either by patient recall or evidence of positive varicella serology). Contraindications include: treatment within the past 3 months with >40 mg prednisolone per day for >1week, >20 mg prednisolone per day for >14 days, MTX >25 mg/week, AZA >3.0 mg/kg/day, or the use of biologic therapy or JAK inhibitors. The vaccine should be given at least 2-4 weeks prior to commencement of biologics or JAK inhibitors. The recently approved non-live sub-unit vaccine (Shingrix) (not currently available in UK) is approved for use in the general population, but has not yet been studied in rheumatology patients or others with auto-immune inflammatory disease. It is not contraindicated in those who are immunosuppressed, although the efficacy and safety of the vaccine has not been evaluated in such patients.

For individuals lacking a history of varicella exposure, then primary immunization with the live varicella vaccine can be considered, assuming there are no contraindications (See those above for use of the live zoster vaccine Zostavax).

There may be a number of women who have not received their MMR vaccine who wish to plan a family. The MMR vaccine is a live vaccine and is contra-indicated for most patients on csDMARD

and/or bDMARD therapy. The need for immunoglobulin should be considered in immunocompromised individuals exposed to varicella or measles who have not been vaccinated or pre-existing immunity cannot be verified (Contact Rheumatology Service). Patients being commenced on synthetic or biologic DMARDs should be asked about potential travel abroad, particularly to places where vaccination against Yellow Fever is required.

The Department of Health Green Book 2017 states that patients taking immunosuppressive agents such as azathioprine >3mg/kg, cyclosporin, methotrexate >25mg, leflunomide, high-dose corticosteroids (>40mg prednisolone per day for more than 1 week or >20mg prednisolone per day or 1mg/kg/day in children under 20kg) for more than 14 days) should avoid live vaccines until at least three months after stopping treatment with these agents.

Those receiving immunoglobulins should be given their vaccinations three months after an infusion of immunoglobulin (donor immunoglobulin may have antibody to measles, varicella and other common viruses and this may prevent replication of the vaccine virus). Exceptions are rubella, BCG and Yellow Fever.

Those receiving cyclophosphamide should avoid live vaccines until at least six months after stopping treatment with this agent.

Vaccinations may be given 1 month off TNFi and abatacept and 6months after rituximab [personal communication with Professor K Winthrop]

Where live vaccination is indicated in patients on biologic or synthetic DMARDs or have received high dose/extended courses of corticosteroids, specialist advice should be obtained from the Consultant Rheumatologist caring for the patient.

Table 1 lists the current live vaccines available in the UK:

Vaccine	**Brand Name**
BCG (including intravesicular use)	Bacillus Calmette-Guerin Vaccine
Nasal Only - Influenza	Note the nasal seasonal influenza vaccine is live - Fluenz®
Measles, Mumps and Rubella Combined Vaccine (MMR)	MMRvaxPRO®, Priorix®
Poliomyeltis (Live oral vaccine)	Poliomyeltis Vaccine, live (oral) GSK OPV
Rotavirus (Live oral vaccine)	Rotarix®
Typhoid (Live oral vaccine)	Vivotif®
Varicella-Zoster Vaccine	Varilrix®, Varivax®, Zostavax® Shingrix®
Yellow Fever	Stamaril®

Non-live Vaccines

Note : Inactivated vaccines cannot replicate and so may be administered to immunosuppressed individuals, although they may elicit a lower response than in immunocompetent individuals.

Table 2, Non-live vaccines

Vaccine	Brand Name
Cholera Vaccine (Oral preparation only)	Dukural®
Diptheria	Given as combined adsorbed diphtheria (low dose), tetanus and inactivated poliomyelitis preparation (Revaxis®).
Hepatitis A	Avaxim®, Epaxal®, Havrix Monodose®, Vaqta Paediatric® With Hepatitis B - Ambirix® and Twinrix® With typhoid - Hepatyrix® and ViATIM®
Hepatitis B	Engerix®, Fendrix®, HBvaxPRO®
Hepatitis A and B Combined	Ambirix®, Twinrix®
Influenza	Aggrippal®, Enzira®, Fluarix®, Fluvirin®, Imuvac®, Influvac® Sub-unit, and Viroflu®
Japanese Encephalitis	Ixiaro®
Meningococcal Group C	Meningitec®, Menjugate Kit®, NeisVac-C®
Meningococcal A,C, W135 and Y conjugate vaccine	Menveo®, Nimenrix®
Meningococcal polysaccharide A,C, W135 and Y vaccine	ACWY Vax®
Pertussis	Diptheria containing vaccine for immunisation of pregnant women against pertussis: Absorbed diphtheria, tetanus, pertussis and poliomyelitis vaccine - Repevax®
Pneumococcal	Pneumovax II® (Adults and Children over 5 years), Prevenar 13®, Synflorix® (Primary childhood immunisation)
Poliomyeltis (Injection)	See under Diptheria vaccine
Rabies	Rabies vaccine - Rab, Rabipur®
Tetanus	*Single preparation no longer available. Combined Adsorbed diphtheria (low dose), tetanus and inactivated poliomyelitis preparation given.
Tick-borne encephalitis	TicoVac®
Typhoid (Polysaccharide injection for vaccination)	Typherix®, Typhim Vi®

Recommended

- **Annual flu vaccine**
- **Every 5 years – pneumococcal vaccine**

Influenza and pneumococcal vaccination should be offered to all patients receiving immunosuppressant therapy (except those on hydroxychloroquine and sulphasalazine).

Pneumococcal vaccine should preferably be given before starting therapy, and should be repeated at 5 years. **No further pneumococcal vaccinations are routinely required after this** [personal communication with Professor K Winthrop].

In patients with recurrent infections, testing of functional antbodies (pneumococcus, haemophilus and influenza) may be helpful. Advice from an immunology consultant should be considered.

Recent research has shown that the majority of patients on csDMARDs and/or biologics (excluding rituximab) receiving annual influenza vaccination will reach sufficient serological immunity to protect against infection. Patients on rituximab (and possibly abatacept) may have a reduced response to influenza vaccine (Kapetanovic et al. 2014).

For more detailed information on immunisation and contra-indications refer to the Department of Health Green Book Website:
https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

Biologics

• A full assessment of vaccination status should be made before commencing treatment with a biologic agent.
• Live vaccines should not be given to patients receiving treatment with biologic agents. Where live vaccination is required it should be given at least 2-4 weeks prior to commencing treatment with a biologic.
• Non–live vaccines may be given, but the immunological response may be reduced. It is therefore recommended that pneumococcal vaccine should be given 2-4 weeks before starting a biologic as response after starting treatment is thought to be reduced.
• Vaccinations may be given 1 month off TNFi and abatacept and 6months after rituximab [personal communication with Professor K Winthrop]
• The datasheet for rituximab recommends avoidance of live vaccination in individuals who are still B cell depleted. Non-live vaccines should ideally be given pre-treatment, as they will be less effective during therapy, and 6 months post infusion where necessary
• Rituximab may reduce titres of protective antibodies so consider checking these, especially in presence of hypogammaglobulinaemia and when otherwise clinically indicated (discuss with Leeds Immunology / Rheumatology if needed)

General Travel Advice

All non-live vaccines should be given as appropriate.

The administration of yellow fever vaccine is contra-indicated in immunosuppressed patients making travel to endemic areas, including tropical Africa and South America inadvisable. A certificate saying Yellow Fever vaccine cannot be given on medical grounds may be acceptable to some immigration authorities in special circumstances. Country requirements are published annually by WHO in International travel and health (available at www.who.int/ith) (WHO, 2004), and are included in Health information for overseas travel (Department of Health, 2001) and may be found on the NaTHNaC, www.nathnac.org.

The parenteral typhoid vaccine offers only 70-80% protection, so personal, food and water hygiene must be emphasised to travellers in endemic areas.

Immunisation with the oral cholera vaccine (Dukoral®) does not provide complete protection. Scrupulous attention to food, water, and personal hygiene is essential when travelling to areas where cholera exists.

Malaria prophylaxis is essential when travelling to countries where there is a risk of developing malaria. Prophylaxis is not absolute and personal protection against being bitten is very important. Patients taking hydroxychloroquine should not take chloroquine as part of their malaria prophylaxis regime. Check for drug interactions with the local Hospital Pharmacy Department.

8. Recommendations for patients undergoing surgical procedures

When elective surgery is planned it has been recommended that a biological DMARD should ideally be stopped for a period of 2 to 5 times the half-life prior to the surgical procedure. Table 3 provides information on the approximate half-lives of currently used biologic medicines. The suggested period for stopping treatment prior to surgery has been agreed as reasonable, given the balance of risk of surgical infection versus the risk of disease flare. The times given are generally agreed to be as short as is safe, with longer periods where there is greater concern. Some surgery may involve much greater risk of infection (eg colonic) whereas others are very low (eg ophthalmic).

Due to inter-patient variability, co-morbidities and the need for rehabilitation post-surgery the period required for interruption of biologic therapy should be discussed with the Rheumatologist well in advance of the planned surgery. The wound should be fully healed and show no evidence infection before the biologic medicine is restarted.

Table 3, Current licensed biological DMARDs half-life's plus suggested stopping period prior to surgery

Drug (bDMARDs)	Dosing interval	Period in which surgery should be scheduled (relative to last biologic dose administered)	One half-life, days	Five half-lives, days
Adalimumab	Every 2 weeks	Week 3	14	70
Abatacept i.v./s.c.	Monthly (i.v.) weekly (s.c.)	Week 5/week 2	14	70
Certolizumab	Every 2 weeks	Week 3	14	70
	Every 4 weeks	Week 5		
Etanercept	Weekly or twice weekly	Week 2	3	15
Golimumab	Every 4 weeks	Week 5	14	70
Infliximab	Every 4, 6 or 8 weeks	Week 5, 7 or 9	9	45
Ixekizumab	Every 4 weeks	Week 5	13	65
Rituximab	Two doses 2 weeks apart, and no more frequent than every 4 months	Months 4–7	18	90
Sarilumab	Every 2 weeks	Week 3	21	105
Secukinumab	Every 4 weeks	Week 5	27	135
Ustekinumab	Every 12 weeks	Week 13	21	105
Tocilizumab i.v.	Every 4 weeks	Week 5		
4mg/kg			11	55
8mg/kg			13	65
Tocilizumab s.c.	Every week /alternate weeks	Week 3	13	65

Drug (tsDMARDs)	Dosing interval	Period in which surgery should be scheduled (relative to last biologic dose administered)	One half-life, days	Five half-lives, days
Apremilast	OD	Week 1	9 hours	45 hours
Baricitinib	OD	Week 1	12.5 hours	62.5 hours
Tofacitinib	OD	Week 1	3 hours	15 hours

9. Guidance on use of DMARDS in pregnancy

	Compatible peri-conception	Compatible with first trimester	Compatible with second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Corticosteroids					
Prednisolone	Yes	Yes	Yes	Yes	Yes
Methylprednisolone	Yes	Yes	Yes	Yes	Yes
Conventional DMARDs					
HCQ	Yes	Yes	Yes	Yes	Yes [a]
MTX	Stop 3 months in advance	No	No	No	Yes [a]
SSZ (with 5mg folic acid)	Yes	Yes	Yes	Yes [b]	Yes [c]
Leflunomide	Cholestyramine washout, no	No	No	No data	Yes [a]
Azathioprine (<2 mg/kg/day)	Yes	Yes	Yes	Yes	yes
Cyclosporin	Yes	Yes [d]	Yes [d]	Yes [a]	Yes [a]
Tacrolimus	Yes	Yes [d]	Yes [d]	Yes [a]	Yes [a]
Cyclophosphamide	No	No [e]	No [e]	No	No
Mycophenalate	Stop 6 weeks in advance	No	No	No	Yes [a]
IVIG	Yes	Yes	Yes	Yes	Yes [a]
Biologic DMARDS					
Anti-TNF					
Infliximab	Yes	Yes	Stop at 16 weeks	Yes [a]	Yes [a]
Etanercept	Yes	Yes	Second but not third	Yes [a]	Yes [a]
Adalimumab	Yes	Yes	Second but not third	Yes [a]	Yes [a]
Certolizumab	Yes	Yes	Yes [a]	Yes [a]	No data

Golimumab	No data	No data	No data	No data	No data
Other biologics					
Abatacept	No	No [f]	No	No data	No data [g]
Anakinra	No	No [f]	No	No data	No data [g]
Belimumab	No	No [f]	No	No data	No data [g]
Ixekizumab	Manufacturer recommends effective contraception during treatment and for at least 10 weeks after treatment	Limited human data – manufacturer advises against use. Animal studies show no direct or indirect harmful on pregnancy, embryonic/ foetal development, parturition or post-natal development.		No human data Individual risk assessment advised	
Rituximab	Stop 6 months in advance	No [f]	No	No data	Yes [a]
Sarilumab	No human data; animal studies show no effect on fertility	No human data. No direct or indirect harmful effects on pregnancy, embryonic/foetal development, parturition or postnatal development. Advice avoid if possible	No human data Advice avoid if possible	No human data Individual risk assessment advised Sarilumab is a large protein and the amount in milk is likely to be very low and absorption is unlikely because it is probably destroyed in the infant's gastrointestinal tract	No human data No effect in animal studies
Secukinumab	No human data; animal studies show no effect on fertility	No human data.	Theoretically transported across	No human data Individual risk assessment advised	No human data

		No direct or indirect harmful effects on pregnancy, embryonic/foetal development, parturition or postnatal development. Advice avoid if possible	the placenta in later pregnancy	Secukinumab is a large protein and the amount in milk is likely to be very low and absorption is unlikely because it is probably destroyed in the infant's gastrointestinal tract	
Tocilizumab	Stop 3 months in advance	No [f]	No	No data	No data [g]
Ustekinumab	Manufacturer recommends contraception during treatment and ≥15 weeks after treatment.	No human data Manufacturer advice avoid during pregnancy. Transplacental transfer not expected in the first trimester but possible theoretical altered placental or maternal physiology	No human data Manufacturer advice avoid during pregnancy. Transplacental transfer not expected in the first trimester but possible theoretical altered placental or maternal physiology	Limited data Use with caution No reports found regarding neonatal toxicity following exposure to ustekinumab. Data suggests that the drug will be excreted in breast milk with unknown effect, this is likely to be in low levels. Manufacturer recommends a decision to discontinue breast feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with ustekinumab must be made taking into account the benefit of breast feeding to the child and the benefit of	No human data

				ustekinumab therapy to the woman.	
Targeted synthetic DMARDS					
Apremilast	No human data; manufacturer recommends contraception throughout treatment.	No human data	No human data	No human data; recommend avoid as considered a small enough molecule that passage into breast milk is possible, with reasonable oral absorption by the infant.	No human data
Baracitinib	Manufacturer recommends use effective contraception during and for at least 1 week after treatment.	No human data – manufacturer advises against use Animal studies show teratogenicity	No human data but animal studies show teratogenicity	No human data; recommend avoid as considered a small enough molecule that passage into breast milk is possible, with reasonable oral absorption by the infant.	No human data – animal studies show no effect
Tofacitinib	Manufacturer advises use effective contraception during treatment and for at least 4 weeks after the last dose.	No human data – manufacturer advises against use. Animal studies show teratogenicity	No human data; parturition and peri/postnatal development affected in animals	No human data; Manufacturer advises breast feeding is contra-indicated. Recommend avoid as considered a small enough molecule that passage into breast milk possible, with oral absorption by the infant.	No human data – animal studies show no effect

For further information and caveats, see relevant recommendations and main text in executive summary and full guideline.

[a] Data are limited.

[b] In healthy full-term infants only.

[c] Conception may be enhanced by stopping SSZ for 3 months prior to conception.

[d] Suggested monitoring of maternal blood pressure, renal function, blood glucose and drug levels.

[e] Only consider in severe or life-/organ-threatening maternal disease.

[f] Unintentional first trimester exposure is unlikely to be harmful.

[g] Unlikely to be harmful.

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