

**YORKSHIRE RHEUMATOLOGY REGIONAL
GUIDELINES FOR THE MONITORING OF
ADULT PATIENTS ON DISEASE MODIFYING
DRUGS (DMARDS)
INCLUDING BIOLOGIC THERAPY**

6th Edition

Revised May 2014

YORKSHIRE RHEUMATOLOGY REGIONAL GUIDELINES FOR DMARD MONITORING

These guidelines have, after extensive discussion with reference to the published literature, been agreed upon by the above group of Rheumatologists. They largely reflect the BSR core guidelines for synthetic and biologic DMARD monitoring. The BSR guidance published in early 2008 is currently undergoing review. 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 GP's 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 contraindications, side effects and drug interactions for both synthetic and biologic DMARDs (<http://www.medicines.org.uk/emc/>).

Under most circumstances drug monitoring and prescribing is best undertaken in General Practice. This is requested by patients and is felt to improve compliance. 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.

These guidelines have now been revised 6 times and will continue to require modification. They are dated and will be reviewed in 2017-8. Suggestions for additions or alterations may be forwarded to:

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Section 1 – Corticosteroids

Corticosteroids are commonly used in the management of a number of rheumatological conditions. Despite their known benefits, prolonged treatment is 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 case 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 food. Alternate day dosing may be deemed appropriate in certain circumstances 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 ASAP.

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 to 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 long term maintenance. 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. EULAR recommends monitoring the following where deemed appropriate: body weight, blood pressure, peripheral oedema, cardiac failure, serum lipids, blood and/or urine glucose and ocular pressure.

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. 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 co-prescribed a calcium and vitamin D supplement. Patients at high risk (previous risk fracture, >65 etc) should start an oral bisphosphonate at the time of commencing steroid therapy. 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 March 2014, National Osteoporosis Guideline Group).

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.

Section 2 - Synthetic or sDMARDs

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 Consider TPMT Consider Hepatitis B and C Consider Pregnancy test
Routine Monitoring:	Repeat FBC/U&E: 2 weekly for 2 months (0-2 months) Monthly for 4 months (2-6 months) Then 3 monthly (assuming dose stable) (*Consider more frequently if high dosage or if renal or hepatic impairment)
Indications for stopping:	Stop medication and contact the Rheumatology service if: WCC <3.5 10 ⁹ /L or below local normal range Neutrophils < 2.0 10 ⁹ /L or below local normal range Platelets <150 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 Diffuse alopecia
Assessment of Response:	Refer to hospital specialist - time to response 6 weeks to 3 months
Additional information:	<ul style="list-style-type: none"> • 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. • Live vaccines should not be administered + avoid for 6 months after stopping. Zoster vaccine may be considered when dosage is low. • 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. <p><u>Important drug reactions:</u></p> <ul style="list-style-type: none"> • 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:	Please contact the Rheumatologist if patient considering conceiving or in case of pregnancy. <ul style="list-style-type: none"> • Azathioprine may be continued during pregnancy and when breastfeeding where the benefit is deemed to outweigh potential risk e.g. in SLE or colitis
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/2881/SPC/Imuran+Tablets+25mg/	

CICLOSPORIN A	
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 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)
Indications for Stopping:	Stop medication and contact the rheumatology service if: BP >160/95 or risen >20mmHg Potassium >5.5mmol/l (especially with ACEi) WCC <3.5 10 ⁹ /L or above local normal range Neutrophils < 2.0 10 ⁹ /L or above local normal range Platelets <150 10 ⁹ /L or above local normal range AST or ALT > 3 times normal range (iu/L) Ankle swelling/Headache (check BP)/Hirsutism Confusion/Tremor/Gingival hyperplasia
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> <ul style="list-style-type: none"> •Drugs which decrease ciclosporin levels (CYP3A4): Barbiturates, carbamazepine, oxcarbazepine, phenytoin; nafcillin, intravenous sulfadimidine, probucol, orlistat, hypericum perforatum (St. John's wort), ticlopidine, sulfapyrazone, terbinafine, bosentan. •Drugs which increase ciclosporin levels (CYP3A4): Macrolide antibiotics,azole antibiotics, amiodarone, diltiazem, verapamil, nifedipine, 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:	Currently not thought to affect fertility and considered safe in pregnancy. Discuss continuation during breast feeding with the Rheumatologist.
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:	<p>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 can 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.</p>
Baseline tests:	<p>FBC/U&E/LFT + consider pregnancy test Urinalysis</p>
Routine Monitoring:	<p>FBC to be performed 10 days after each pulse (nadir result) Urinalysis WCC <3.5 10⁹/L or below local normal range Neutrophils < 2.0 10⁹/L or below local normal range Platelets <150 10⁹/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.</p>
Indications for stopping:	<p>Contact local rheumatology service if: WCC < 3.5 10⁹/L , Neutrophils < 2.0 10⁹/L, Platelets <150 10⁹/L Oral ulceration/unusual bruising/rash/fever/cough or shortness of breath/nausea/alopecia</p>
Assessment of response:	<p>Defined by the Rheumatology Consultant according to the disease/organ affected. An interim review should be performed after the first 3 pulses and full assessment after completion of 6.</p>
Additional information:	<p>Infection to be excluded before administration of each infusion. 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 Caution - tofacitinib Oral hypoglycaemics may be potentiated by cyclophosphamide.</p>
Pregnancy & Breastfeeding:	<p>The Rheumatologist will discuss with the patient the potential effects on fertility before commencing therapy. Pregnancy should be avoided during treatment and for 3 months after discontinuation of treatment. Breastfeeding not recommended</p>
<p>Refer to the Rheumatologist and the Hospital Medicines Information Department for more detailed prescribing information.</p>	

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:	<ul style="list-style-type: none"> • FBC • U&E • LFT • Urinalysis • Baseline chest X-ray (consider annual repeat) <p>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.</p>
Routine Monitoring:	<ul style="list-style-type: none"> • 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 3 monthly in long term stable users. • <u>Urinalysis must be done before each injection.</u>
Indications for Stopping Therapy:	<p>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:</p> <p>WCC <3.5 10⁹/L or below local normal range Neutrophils < 2.0 10⁹/L or below local normal range Platelets <150 10⁹/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). <u>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).</u></p>
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:	<p>Contra-indicated - Gross renal or hepatic disease, history of blood dyscrasias, exfoliative dermatitis and systemic lupus erythematosus (SLE).</p> <p><u>Important drug reactions:</u></p> <ul style="list-style-type: none"> • 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) • Phenylbutazone or oxyphenbutazone (use with caution)
Pregnancy & Breastfeeding:	Avoid in pregnancy and breastfeeding as safety has not been established.
<p>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/</p>	

HYDROXYCHLOROQUINE	
Dose:	Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight. Usually started at a dose of 200mg bd for the first 3 months and then reduced to 200mg daily as a maintenance dose if effective (aim for 3-5mg/kg/day using ideal bodyweight especially when obese)
Baseline tests:	Routine blood/urine monitoring test are not necessary other than: <ul style="list-style-type: none"> • FBC/U&E/LFT • Ophthalmological screening recommended if pre-existing ocular pathology and especially any retinal condition Impaired renal function and over the age of 70 Not generally recommended where pre-existing maculopathy of the eye.
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 visual acuity/fundoscopy. Formal ophthalmological screening is suggested when: After 7 years of continuous treatment or more than 500grams of HCQ in total has been taken – whichever is first If doses of > 6.5mg/kg/day are used (=> 400mg/day for 60kg patient)
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
Assessment of Response:	For rheumatic disease treatment should be discontinued if there is no improvement by 6 months.
Additional information:	Patients with quinine sensitivity. Use in caution in patients with: <ul style="list-style-type: none"> • Psoriasis - increased risk of flare • Patients taking medicines which may cause adverse ocular/skin reactions 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:	Generally thought to be safe in pregnancy and breastfeeding
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/6977/SPC/Plaquenil+Tablets/	

LEFLUNOMIDE	
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Dose:	Usually considered for patients with active RA/ PsA who have failed methotrexate and sulphasalazine. Loading dose of 100mg daily for three days IS NOT recommended 20mg (or 10mg) 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 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:	2 Weekly FBC/LFT and BP for 2 months (0 - 2) Monthly for 4 months (2-6) Then 3 monthly (stable dose)
Indications for stopping treatment:	<ul style="list-style-type: none"> • 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 – stop and contact hospital specialist. • Abnormal LFT's – ALT greater than 3 x the upper limit of normal, stop medication, consider washout and contact hospital specialist. <p>In addition, Stop medication and hospital specialist if:</p> <ul style="list-style-type: none"> • WCC <3.5 10⁹/L or below local normal range • Neutrophils < 2.0 10⁹/L or below local normal range • Platelets <150 10⁹/L or below local normal range • 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) Live vaccines must not be administered. Avoidance of alcohol recommended <u>Important drug interactions:</u> hepatotoxic/haemotoxic drugs, cholestyramine, rifampicin, warfarin, tolbutamide and phenytoin. Contains lactose and soya lecithin – avoid in lactose, soya or peanut allergy.
Pregnancy & Breastfeeding:	Effective contraception should be used in both males and females. Females should use reliable contraceptive measures for 2 years after stopping treatment (if impracticable to wait refer to datasheet with regards to wash-out and monitoring of plasma levels). Men wishing to conceive should perform a washout – see datasheet regime plus monitoring of plasma levels. Breastfeeding is not recommended
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 <u>day</u> of administration plus <u>strength</u> 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 is increased when fibrosis is present).
Routine Monitoring:	Repeat FBC/LFT 2 weekly for 2 months (0-2), then monthly for 4 months (2-6) and then 3 monthly unless dose changes + U&Es when clinically indicated NPSA MTX monitoring books for all patients remain recommended (Consider increasing the frequency of monitoring if psoriatic arthritis, diabetes, obesity, uncertain alcohol intake or concomitant medication which may reduce the renal excretion of methotrexate).
Indications for Stopping Therapy:	Stop medication and contact local rheumatology service if: WCC < 3.5 10 ⁹ /L or below local normal range Neutrophils < 2.0 10 ⁹ /L or below local normal range Platelets < 150 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 folic 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. Caution when pre-existing haematological condition Caution - underlying chest disease/smoker Where history of excessive alcohol intake Drug interactions: Avoid live vaccines (zoster safe if weekly MTX dose 20mg or less) Concomitant administration of folate antagonists such as trimethoprim, cotrimoxazole and nitrous oxide should be avoided 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 and the infection has resolved) Acitretin - severe hepatitis reported when combined with MTX Vitamin preparations containing folic acid
Pregnancy & Breastfeeding:	Adequate contraception should be used by women and continued for at least 3 months after stopping treatment with methotrexate. Contra-indicated in breast feeding. If pregnancy occurs during treatment with methotrexate immediately contact the Rheumatology Service for appropriate advice.
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 – starting dose 500mg nocte week 1, 500mg twice daily week 2, 500mg mane and 1g nocte week 3 and then 1g twice a day. If there is gastric intolerance considering giving as 500mg four times a day. If indicated the dose may be increased to 1.5g twice a day (max 40mg/kg/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).
Baseline tests:	Hepatitis B and C Varicella immune status (avoid if re-current herpes/shingles) FBC/U&E/LFT/lipids and BP Consider PCI / GFR or creatinine clearance Consider Pregnancy Test
Routine monitoring:	At week one: FBC/U&E/LFT Then 2 weekly for 2 months (0-2 months), Then monthly for 4 months (2-6 months), Then 3 monthly +/- Lipids
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: WCC <3.5 10 ^{*9} /L or below local normal range Neutrophils < 2.0 10 ^{*9} /L or below local normal range Platelets <150 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. Live vaccines must not be given 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. Important drug interactions: 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:	Exclude pregnancy before starting treatment. Use contraception during therapy and for 6 weeks after stopping. Breastfeeding is not recommended. 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/1679/SPC/Cellcept+250mg+Capsules/	

PENICILLAMINE	
Dose:	<p>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 :</p> <ul style="list-style-type: none"> • 250mg tablet daily for 1 week • 375mg daily for 1 week • Then two 250mg tablets daily <p>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).</p> <p>Consider co-administration of pyridoxine if treatment is continued long term.</p>
Baseline Tests:	<p>Urinalysis FBC/U&E</p>
Routine Monitoring:	<p>Two weekly for the first 2 months (0-2 months) Monthly for 4 months (2-6 months) Thereafter 3 monthly (unless dose changes)</p>
Indications for Stopping Therapy:	<p>Stop and contact local rheumatology service if:</p> <ul style="list-style-type: none"> • WCC <3.5 10⁹/L or below local normal range • Neutrophils < 2.0 10⁹/L or below local normal range • Platelets <150 10⁹/L or below local normal range • Proteinuria/Blood >1+ <p>Rash - Antihistamines/steroid cover/temporary reduction in dose can control urticarial 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)</p>
Assessment of Response:	4-6 months
Additional information:	<p>Contra-indicated when:</p> <p>SLE</p> <p>Previous agranulocytosis, aplastic anaemia or severe thrombocytopenia in association with penicillamine.</p> <p>Moderate or severe renal impairment.</p> <p>Drug interactions:</p> <ul style="list-style-type: none"> • 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.
<p>Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/emc/medicine/9211/SPC/Distamine+125mg+Film-coated+tablets/</p>	

SULFASALAZINE	
Dose:	Indications include - Rheumatoid arthritis, psoriatic arthritis and inflammatory bowel disease. Gradual dose titration to avoid gastric intolerance (enteric coated prep suggested): 500mg nocte week 1, 500mg twice a day week 2, 500mg mane and 1g nocte week 3 and 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 (max 40mg/kg/day).
Baseline tests:	FBC LFTs U&E Serum folate
Routine monitoring:	FBC and LFT: 2 weekly for 2 months (0-2 months), monthly for 4 months (2-6 months) then 3 monthly. U&E : monthly for first 3 months and then if clinically indicated. Monitoring may be discontinued after 2 years 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: <ul style="list-style-type: none"> • WCC <3.5 10⁹/L or below local normal range • Neutrophils < 2.0 10⁹/L or below local normal range • Platelets <150 10⁹/L or below local normal range • Proteinuria/Blood >1+
Assessment of response:	At 3-6 months
Additional information:	<ul style="list-style-type: none"> • 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 dyscrasias 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. <p><u>Important drug reactions:</u> •azathioprine/mercaptopurine – increased bone marrow suppression •digoxin (decreased absorption) •Hypoglycaemic agents – increased hypoglycaemia</p>
Pregnancy & Breastfeeding:	Where deemed appropriate continue in pregnancy, but combine with folic acid 5mg od. Considered safe when breast feeding.
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/10722/SPC/Salazopyrin+En-Tabs/	

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 ANCA positive vasculitis and also in the management of SLE.

Clinical Commissioning Policy: Rituximab for Antineutrophil Cytoplasmic Antibody Associated Vasculitis, April 2013 ref: NHSCB/A13/P/a (<http://www.england.nhs.uk/wp-content/uploads/2013/04/a13-p-a.pdf>)

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's 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, etanercept, golimumab and infliximab (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, there are also now four other licensed bDMARDs available in the UK: abatacept, belimumab, tocilizumab and rituximab (please refer to table 2).

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

Adalimumab (Humira®)	Etanercept (Enbrel®)	Certolizumab (Cimzia®)	Golimumab (Simponi®)	Infliximab (Remicade®)
Humanised monoclonal antibody	P75 fc fusion protein	Fab fragment	Humanised monoclonal antibody	Chimeric human/ marine antibody
Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Intravenous infusion
Licensed for: RA JIA PsA Axial spondyloarthritis AS Crohn's UC	Licensed for: RA JIA PsA AS Plaque psoriasis	Licensed for: RA Axial spondyloarthritis AS PsA	Licensed for: RA + MTX PsA +/- MTX AS UC	Licensed for: RA+MTX PsA +/- MTX AS Psoriasis Crohns UC

Non-TNFi licensed biologic DMARDs:

Abatacept is a fusion protein which moderates T lymphocyte-dependent antibody responses and inflammation. It is licensed in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis. NICE supports its use as a first line bDMARD or following sDMARD failure, in the management of RA (TA234). It may also be used in patients who have failed a first line biologic (TA195) and have a primary contra-indication or adverse reaction to rituximab (TA195).

Belimumab is the first licensed biologic for the management of SLE. It is a human, IgG1 λ monoclonal antibody and blocks the action of BLYS (B Lymphocyte Stimulator Protein). It is indicated as an additional therapy in adult patients with active, autoantibody positive SLE with a high degree of disease activity despite standard therapy. It has not been studied in severe active CNS lupus or severe active lupus nephritis and is not recommended for these conditions. Its use is currently not supported by NICE and applications for individual funding should be made to the NHS Commissioning Board.

Tocilizumab (RoActemra) is the first IL-6 directed bDMARD (acting as an IL 6 receptor antagonist) to become licensed in Europe for the management of moderate to severe rheumatoid arthritis, with or without methotrexate. Interleukin-6 (IL-6) is a multifunctional cytokine that has a wide range of biological activities in various target cells and regulates immune responses, acute phase reactions, haematopoiesis and bone metabolism. Current NICE guidance only approves the use of tocilizumab in combination with methotrexate. NICE supports its use as a first line bDMARD following sDMARD failure in the management of RA (TA234). It may also be used

in patients who have failed a first line bDMARD (TA195) or primary contra-indication or adverse reaction to rituximab (TA195). NICE also supports use following treatment failure with rituximab. EULAR guidance recognises that there may be a proportion of patients who are unable to tolerate methotrexate and are likely to gain clinical benefit from tocilizumab monotherapy (Smolen et al. Ann Rheum Dis 2013).

Table 2, Non-TNF biologic medicines

Abatacept (Orencia®)	Belimumab (Benlysta®)	Rituximab (Mabthera®)	Tocilizumab (RoActemra®)
Fusion protein – blocks T cell activation	human, IgG1λ monoclonal antibody - blocks action of BLYS	Monoclonal antibody – CD20 B cell depletion	Monoclonal antibody against soluble and membrane IL-6 receptor
Licensed for: Moderate to severe RA following DMARD failure (with MTX) Polyarticular JIA	Licensed for: Add on therapy active autoantibody positive SLE with high disease activity (excluding CNS and lupus nephritis)	Licensed for: RA (with MTX) following DMARD + TNFi failure GPA with glucocorticoids NHL CLL	Licensed for: RA (+/-MTX) following DMARD failure sJIA (+/- MTX) Juvenile Idiopathic polyarthritis

Due to tocilizumab's mode of action its use is most commonly associated with a fall in the white cell count and neutrophil count and occasionally platelets. It also commonly affects liver function tests (raised transaminases). Elevated lipid levels including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides have been reported with all bDMARDs, but especially Tocilizumab. However the atherogenic index has been shown to remain stable and no impact on CVS outcome has been proven. Full blood counts, liver function tests and lipid parameters should be monitored. IL-6 has been associated with suppression of the CP450 hepatic system (CYP1A2, CYP2C9, CYP2C19, and CYP3A4) and as a consequence of this the use of tocilizumab has been associated with an increase in metabolism of the following medicines: statins (simvastatin, atorvastatin and lovastatin), calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporine, and benzodiazepines. The doses of these medicines may require adjustment in patients receiving tocilizumab.

Rituximab is licensed for the treatment of severe active RA, in combination with methotrexate, in patients who have had an inadequate response or intolerance to other DMARDs, including one or more tumour necrosis factor (TNF) inhibitor therapies. NICE approves its use in RA, in combination with methotrexate, where there has been treatment failure or an adverse drug reaction to the first biologic agent used. At present NICE does not recognise sero-negative RA as a relative contra-indication to treatment with rituximab. In the management of RA rituximab has been combined with alternative DMARDs. Prior to the formation of the CCG's, the Yorkshire and Humber Specialised Commissioning Group agreed to fund treatment with rituximab

in combination with an alternative sDMARD for the management of rheumatoid arthritis. The commissioning policy also permitted a single cycle of rituximab monotherapy with an IFR being submitted for subsequent cycles. EULAR recently acknowledged that in the presence of certain contra-indications to use of other biologic agents (recent history lymphoma, latent TB where chemoprophylaxis contra-indicated, history of demyelinating disease) it might be appropriate to use rituximab following sDMARD failure alone. Some centres are now using a reduced dosage regime for rituximab (outside of the product license) following the first cycle, where there has been both an adequate clinical response and B cell depletion. Please refer to individual hospital formulary dosage recommendations for rituximab in RA.

Rituximab is also used in the management of a number of connective tissue diseases (CTD) and now holds a license for the management of severe, active Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) in combination with steroids. Please refer to local hospital guidance with regards to permitted use in CTD. Some centres are using Rituximab in the same dosing schedule in CTD's as for RA and vasculitis (2 one gram infusions 2 weeks apart), while others use the standard haematological protocol of 4 infusions.

Treatment with TNF inhibitors (safety issues)

Treatment for patients with active RA, PsA, Psoriasis or AS where NICE approval exists. For RA this is when two or more sDMARDs have failed (including methotrexate), and 2 BSR assessments for activity of RA (DAS 28 >5.1) have been done more than 4 weeks apart, to establish eligibility. For PsA only one assessment is needed to assess disease activity. In AS where two or more NSAID'S have failed, etanercept and adalimumab have NICE approval, but 2 clinical assessments of disease activity at least 12 weeks apart are required.

1) General contraindications (discuss with relevant specialist)

- Pregnancy / Breastfeeding (though early data is very reassuring)
- 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 etanercept + 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)
- Induction of autoimmunity
- Interaction with anikinra
- AVOID Live Vaccines (SEE VACCINES SECTION)**

ABATACEPT (ORENCIA®) – Bristol Myers Squibb Pharmaceuticals Limited	
Therapeutic class:	Fusion protein which moderates T lymphocyte-dependent antibody responses and inflammation (see p17)
Licensed Dose:	RA (+methotrexate) ● subcutaneous route - give 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 - following DMARD failure alone, with mtx http://guidance.nice.org.uk/TA280/Guidance/pdf/English RA - following failure DMARDs and biologic failure with mtx http://guidance.nice.org.uk/TA195/Guidance/pdf/English
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.
Pregnancy & Breastfeeding:	Please contact the Rheumatologist if patient considering conceiving or in case of pregnancy. <ul style="list-style-type: none"> • Females to use adequate contraception during and for 14 weeks after the last dose. • Breastfeeding is not recommended until 14 weeks after the 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:	<ul style="list-style-type: none"> • Full clinical/infection screen • Urinalysis & BP • FBC/U&E/LFT/ANA/DNA • CXR (evidence TB/fibrosis) • Quantiferon or TB spot (as indicated) • Hepatitis B&C + consider 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 months and then 3 monthly intervals
Indications for Stopping Therapy:	Stop treatment if: <ul style="list-style-type: none"> ●Evidence of active infection ●Pruritis/rash or symptoms suggestive of an allergic reaction WCC <3.5 10 ⁹ /L or below local normal range Neutrophils < 2.0 10 ⁹ /L or below local normal range Platelets <150 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/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®) - Abbott Laboratories Limited	
Therapeutic Class:	Biologic - TNF α Inhibitor
Licensed Indications:	Adalimumab is licensed for the following rheumatological conditions: <ul style="list-style-type: none"> • 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 TA130 + TA195 http://guidance.nice.org.uk/TA130/Guidance/pdf/English http://guidance.nice.org.uk/TA195/Guidance/pdf/English PsA TA199 http://guidance.nice.org.uk/TA199/Guidance/pdf/English AS TA143 http://guidance.nice.org.uk/TA143/Guidance/pdf/English
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	<ul style="list-style-type: none"> • Live vaccines must not be given • 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.
Pregnancy & Breastfeeding:	Please contact the Rheumatologist if patient considering conceiving or in case of 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.
Baseline Tests:	<ul style="list-style-type: none"> • Full clinical/infection screen • Urinalysis & BP • FBC/U&E/LFT/ANA/DNA • CXR (evidence TB/fibrosis) • Quantiferon or TB spot when indicated • Hepatitis B and C + consider HIV • Pregnancy test if indicated
Routine Monitoring:	<ul style="list-style-type: none"> • Usual tests for methotrexate or other DMARD • If monotherapy FBC/LTF at 1,3 and 6 months, then 3 monthly • ANA yearly
Indications for Stopping Therapy:	Stop if: <ul style="list-style-type: none"> • 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 WCC < 3.5 $10^9/L$ or below local normal range Neutrophils < 2.0 $10^9/L$ or below local normal range Platelets < 150 $10^9/L$ 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/21201/SPC/Humira+Pre-filled+Pen%2c+Pre-filled+Syringe+and+Vial/#FORM	

BELIMUMB (BENLYSTA®) - Glaxosmithkline	
Therapeutic class:	Belimumab is a human, IgG1 λ monoclonal antibody - blocks action of BLyS (B Lymphocyte Stimulator Protein) see p17.
Licensed Indications:	Add on therapy in adult patients with active, autoantibody positive SLE with a high degree of disease activity despite standard therapy (*has not been studied in severe active CNS lupus or severe active lupus nephritis and is not recommended)
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:	In progress - Original FAD did not recommend belimumab, however this is under appeal.
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	<ul style="list-style-type: none"> ●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:	<p>Please contact the Rheumatologist if patient considering conceiving or in case of pregnancy.</p> <ul style="list-style-type: none"> • 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:	<ul style="list-style-type: none"> • Full clinical/infection screen • Urinalysis & BP • FBC/U&E/LFT/ANA/DNA • B Cell FACS analysis • Immunoglobulins • CXR • Hepatitis B&C • Pregnancy test if indicated • Consider TB screening (not done routinely)
Routine Monitoring:	<ul style="list-style-type: none"> ●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:	<p>Stop treatment if:</p> <ul style="list-style-type: none"> ●Evidence of active infection ●Hypersensitivity reaction ●Leucopenia (WCC <3.5 10⁹/L, Neut < 2.0 10⁹/L or local ranges) ●Increased insomnia/change in mood <p>CONTACT THE RHEUMATOLOGY SERVICE</p>
<p>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/</p>	

CERTOLIZUMAB PEGOL (CIMZIA®) - UCB Pharma Limited	
Therapeutic Class:	Biologic - TNF α Inhibitor
Licensed Indications:	RA in combination with methotrexate (datasheet permits use without methotrexate where there is intolerance)
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 <u>Missed dose:</u> 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:	DMARD failure with or without mtx http://guidance.nice.org.uk/TA186 Following 1st line biologic failure where AE to rituximab or primary contra-indication to rituximab http://guidance.nice.org.uk/TA195/Guidance/pdf/English
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	<ul style="list-style-type: none"> ● 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
Pregnancy & Breastfeeding:	Please contact the Rheumatologist if patient considering conceiving or in case of pregnancy. <ul style="list-style-type: none"> ● Women childbearing potential - continue adequate contraception during treatment and for 5 months after stopping. ● Not recommended in pregnancy ● Breastfeeding - insufficient information (Contact the Hospital Pharmacy Medicines Information Department)
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:	<ul style="list-style-type: none"> ● Full clinical/infection screen ● Urinalysis & BP ● FBC/U&E/LFT/ANA/DNA ● CXR (evidence TB/fibrosis) ● Quantiferon or TB spot (as indicated) ● Hepatitis B&C + consider HIV ● Pregnancy test if indicated
Routine Monitoring:	Continue standard DMARD monitoring, if monotherapy FBC/LFT at 1, 3 and 6 months then 3 monthly + ANA yearly
Indications for Stopping Therapy:	Stop if: <ul style="list-style-type: none"> ● Evidence of infection ● Query demyelination ● SLE or new autoimmune syndrome ● Severe injection site reaction (If minor reaction try oral anti-histamine or topical corticosteroids) WCC < 3.5 $10^9/L$ or below local normal range Neutrophils < 2.0 $10^9/L$ or below local normal range Platelets < 150 $10^9/L$ 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®) - Pfizer Limited	
Therapeutic Class:	Biologic - TNF α Inhibitor
Licensed Indications:	<p>Etanercept is licensed for the following rheumatological conditions:</p> <ul style="list-style-type: none"> • 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:	<p>RA TA130 + TA195 http://guidance.nice.org.uk/TA130/Guidance/pdf/English http://guidance.nice.org.uk/TA195/Guidance/pdf/English PsA TA199 http://guidance.nice.org.uk/TA199/Guidance/pdf/English AS TA143 http://guidance.nice.org.uk/TA143/Guidance/pdf/English JIA TA35 http://guidance.nice.org.uk/TA35/Guidance/pdf/English (4-17 years only)</p>
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	<ul style="list-style-type: none"> • 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. <p>*Patients treated with etanercept should be given the Patient Alert Card. **May be preferred TNFi where previous TB contact but no active infection.</p>
Pregnancy & Breastfeeding:	<p>Please contact the Rheumatologist if patient considering conceiving or in case of pregnancy.</p> <ul style="list-style-type: none"> • Breastfeeding - insufficient information (Contact the Hospital Pharmacy Medicines Information Department)
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:	<ul style="list-style-type: none"> • Full clinical/infection screen • Urinalysis & BP • FBC/U&E/LFT/ANA/DNA • CXR (evidence TB/fibrosis) • Quantiferon or TB spot (as indicated) • Hepatitis B&C + consider HIV • Pregnancy test if indicated
Routine Monitoring:	Continue standard DMARD monitoring, if monotherapy FBC/LFT at 1, 3 and 6 months then 3 monthly + ANA yearly
Indications for Stopping Therapy:	<p>Stop if:</p> <ul style="list-style-type: none"> • Evidence of infection • Possible demyelination • SLE or other autoimmune syndrome • Severe injection site reaction (If minor reaction try oral anti-histamine or topical corticosteroids) <p>WCC < 3.5 $10^9/L$ or below local normal range Neutrophils < 2.0 $10^9/L$ or below local normal range Platelets < 150 $10^9/L$ or below local normal range AST or ALT > 3 times normal range (iu/L)</p> <p>CONTACT THE RHEUMATOLOGY SERVICE</p>
<p>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/</p>	

GOLIMUMAB (SIMPONI®) - Merck Sharp & Dohm	
Therapeutic Class:	Biologic - TNF α 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. <u>Increased dose:</u> In 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. <u>Missed dose:</u> 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 http://guidance.nice.org.uk/TA225 http://guidance.nice.org.uk/TA224 PsA http://guidance.nice.org.uk/TA220 AS http://guidance.nice.org.uk/TA233
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	<ul style="list-style-type: none"> ● 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.
Pregnancy & Breastfeeding:	Please contact the Rheumatologist if patient considering conceiving or in case of pregnancy. Women childbearing potential - continue adequate contraception during treatment and for 6 months after stopping. Infants exposed to golimumab in utero should not be given live vaccines for 6 months following the mother's last golimumab injection during pregnancy. Breastfeeding not recommended - 6 months should elapse from last injection.
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:	<ul style="list-style-type: none"> ● Full clinical/infection screen ● Urinalysis & BP ● FBC/U&E/LFT/ANA/DNA ● CXR (evidence TB/fibrosis) ● Quantiferon or TB spot (as indicated) ● Hepatitis B&C +consider HIV ● Pregnancy test if indicated
Routine Monitoring:	Continue standard DMARD monitoring, if monotherapy FBC/LFT at 1, 3 and 6 months then 3 monthly + ANA yearly
Indications for Stopping Therapy:	<p>Stop if:</p> <ul style="list-style-type: none"> ● Evidence of infection ● Possible demyelination ● SLE / autoimmune syndrome ● Severe injection site reaction (If minor reaction try oral anti-histamine or topical corticosteroids) <p>WCC < 3.5 $10^9/L$ or below local normal range Neutrophils < 2.0 $10^9/L$ or below local normal range Platelets < 150 $10^9/L$ or below local normal range AST or ALT > 3 times normal range (iu/L)</p> <p>CONTACT THE RHEUMATOLOGY SERVICE</p>
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®) - Merck Sharp & Dohme Limited	
Therapeutic Class:	Biologic - TNF α Inhibitor (chimeric human-murine IgG1 monoclonal antibody)
Licensed Indications:	Infliximab is licensed for the following rheumatological conditions: 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). 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.
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 TA130 + TA195 http://guidance.nice.org.uk/TA130/Guidance/pdf/English http://guidance.nice.org.uk/TA195/Guidance/pdf/English PsA TA199 http://guidance.nice.org.uk/TA199/Guidance/pdf/English AS TA143 http://guidance.nice.org.uk/TA143/Guidance/pdf/English (Note: NICE has not approved use in AS)
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	<ul style="list-style-type: none"> ● 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.
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:	<ul style="list-style-type: none"> ● Full clinical/infection screen ● Urinalysis & BP ● FBC/U&E/LFT/ANA/DNA ● CXR (evidence TB/fibrosis) ● Quantiferon or TB spot (as indicated) ● Hepatitis B&C + consider HIV ● Pregnancy test if indicated
Routine Monitoring:	Continue standard DMARD monitoring FBC/LFT/U&E at 1, 3 and 6 months then 3 monthly + ANA yearly + Urinalysis before each infusion
Indications for Stopping Therapy:	Stop if: <ul style="list-style-type: none"> ● Evidence of infection ● Query demyelination ● SLE or other autoimmune syndrome ● Severe injection site reaction (If minor reaction try oral anti-histamine or topical corticosteroids) WCC <3.5 10 ⁹ /L or below local normal range Neutrophils < 2.0 10 ⁹ /L or below local normal range Platelets <150 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/3236/SPC/Remicade+100mg+powder+for+concentrate+for+solution+for+infusion/	

RITUXIMAB (MABTHERA®) - Roche Products Limited	
Therapeutic class:	Rituximab - chimeric mouse/human monoclonal antibody, binds to transmembrane antigen CD20 resulting in B cell lysis (see p17)
Licensed Indications:	<p>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)</p> <p>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.</p>
Licensed Dose:	<p>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).</p> <p>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). IV Methylprednisolone for 1 to 3 days at a dose of 1000 mg per day is recommended 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.</p> <p>Repeat Dosing – Ususally 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.</p>
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:	<p>http://guidance.nice.org.uk/TA195/Guidance/pdf/English</p> <p>Clinical Commissioning Policy: Rituximab for ANCA Associated Vasculitis, April 2013: NHSCB/A13/P/a http://www.england.nhs.uk/wp-content/uploads/2013/04/a13-p-a.pdf</p> <p>Clinical Commissioning Policy: Rituximab for the treatment of Systemic Lupus Erythematosus (SLE), September 2013: NHS England A13/PS/a (http://www.england.nhs.uk/wp-content/uploads/2013/09/a13-psa.pdf)</p>
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	<ul style="list-style-type: none"> ●Hypersensitivity to the active substance/excipients (incl. murine proteins) ●Severe heart failure (NYHA IV) or severe, uncontrolled cardiac disease ●Active, severe infections ●Severely immunocompromised ●Live vaccines (immunise 4 weeks prior to treatment – SEE SECTION 4)
Pregnancy & Breastfeeding:	Please contact the Rheumatologist if patient considering conceiving or in case of pregnancy.
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 6 months). 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 sDMARD continue routine monitoring for concomitant therapy. Before each infusion ●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 - discuss case with Leeds Service ● If unsure contact local rheumatology service.

Please refer to licensed datasheet for more comprehensive prescribing information:

<http://www.medicines.org.uk/EMC/medicine/2570/SPC/Mabthera+100mg+and+500mg+concentrate+for+solution+for+infusion/>

TOCILIZUMAB (RoACTEMRA®) - Roche Products Limited	
Therapeutic Class:	Biologic - humanised IgG1 monoclonal antibody against the human interleukin-6 (IL-6) receptor (see p17)
Licensed Indications:	RA (with or without MTX)
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 <u>AOSD</u> use the same dose as recommended for sJIA). Important - refer to datasheet for dosage adjustment or interruption when abnormal LFT's, neutrophils or platelets.
Preparation:	<ul style="list-style-type: none"> 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:	<u>In combination with methotrexate</u> - first line following sDMARD failure or after TNFi failure and a primary contra-indication to rituximab or rituximab AE or following rituximab treatment failure http://guidance.nice.org.uk/TA247/Guidance/pdf/English
Warnings/Contra-indications/Significant drug interactions: (*Refer to licensed datasheet for special warnings)	<ul style="list-style-type: none"> 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 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. <p>*All patients treated with RoActemra should be given the Patient Alert Card.</p>
Pregnancy & Breastfeeding:	Please contact the Rheumatologist if patient considering conceiving or in case of pregnancy. Women of childbearing potential -continue adequate contraception during therapy and for 3 months after stopping. Should not be used in pregnancy, unless clearly necessary (animal studies associated with spontaneous abortion at high dose) Breastfeeding - risk unknown (Contact the Hospital Pharmacy Medicines Information Department)
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:	<ul style="list-style-type: none"> Full clinical/infection screen Urinalysis & BP FBC/U&E/LFT/ANA/DNA (contraindicated if LFT's > 5*ULN or absolute neutrophil count $2.0 < 10^9/l$) CXR (evidence TB/fibrosis) Quantiferon or TB spot (as indicated) Hepatitis B&C + consider HIV Baseline lipids Pregnancy test if indicated
Routine Monitoring:	As for DMARD therapy or <ul style="list-style-type: none"> LFT's (Transaminases) monthly Neutrophils and Platelets - monthly Lipid parameters - assessment of lipid parameters at 3 months U&E's plus urinalysis before each infusion.
Indications for Stopping Therapy:	Stop if: <ul style="list-style-type: none"> *Infusion reaction Evidence of infection Development of new abdominal symptoms Deterioration in lung function (perform CXR / PFT) LFT's transaminases persistently > 3*ULN Neutrophils < $1.0 * 10^9/l$ Platelets < $100 * 10^3/\mu l$ Macrophage activation syndrome (MAS) reported in sJIA <p>CONTACT THE RHEUMATOLOGY SERVICE</p> <p>*Mild infusion reaction common within 24 hours of the first infusion. Severe reaction may be observed between 2nd to 5th infusion</p>
Please refer to licensed datasheet for more comprehensive prescribing information: http://www.medicines.org.uk/EMC/medicine/22311/SPC/RoActemra+20mg+ml+Concentrate+for+Solution+for+Infusion/	

Section 4 - Additional information

4.1 Guidance on vaccination in patients receiving sDMARDs and/or bDMARDs

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.

Vaccination status should be evaluated before commencing treatment with most DMARDs (except HCQ, SSA and Gold), and especially bDMARDs. It is suggested that varicella immune status should be established in those starting immunosuppression and on occasion even close household contacts. If the need for vaccination with Varicella is identified, this should ideally be administered at least 2 weeks prior to commencement. However in patients already taking MTX or AZA in standard doses, giving Zostavax® is thought to be safe (BSR guidance 2014). It should be noted that rarely the varicella-zoster vaccine virus has been transmitted from the vaccinated individual to close contacts.

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 sDMARD 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 states that patients taking immunosuppressive agents such as azathioprine, cyclosporin, methotrexate, cyclophosphamide, leflunomide and the newer cytokine inhibitors (alone or in combination with lower doses of steroids) should avoid live vaccines until at least six months after stopping treatment with these agents. In addition, care should be taken in patients receiving systemic high-dose steroids. The DOH guidance 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. Individuals receiving prolonged oral corticosteroid treatment at lower doses may also be at risk. 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®
Poliomyelitis (<u>Live oral vaccine</u>)	Poliomyelitis Vaccine, live (oral) GSK OPV
Rotavirus (<u>Live oral vaccine</u>)	Rotarix®
Typhoid (<u>Live oral vaccine</u>)	Vivotif®
Varicella-Zoster Vaccine	Varilrix®, Varivax®, Zostavax®
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 (<u>Oral preparation only</u>)	Dukoral®
Diphtheria	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	Diphtheria 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)
Poliomyelitis (<u>Injection</u>)	See under Diphtheria 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 (<u>Polysaccharide injection for vaccination</u>)	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. . Pneumococcal vaccine should preferably be given before starting therapy, but if not it should be repeated at 5 yearly intervals (rather than 10 year intervals). The need for repeat pneumococcal vaccination at 5 year intervals is based on expert recommendations from Microbiologists. Recent research has shown that the majority of patients on sDMARDs 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 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.
- On stopping treatment with a biologic agent current **DOH guidance recommends waiting for 6 months** before administering a live vaccine. It should be noted that the datasheet for abatacept suggest live vaccination is acceptable after 3 months have elapsed. Please contact the Rheumatologist for

advice if a live vaccine is indicated in a patient currently on a DMARD or biologic medicine or where the medication has been stopped for less than 6 months.

- 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 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 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.

4.2 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

Biologic	Terminal Half-life (per licensed datasheet)	Minimum suggested stopping period prior to surgery
Etanercept (Embrel®)	70 hours	1-2 weeks
Abatacept (Orencia®)	Subcutaneous 14.3 days Intravenous 13.1 days	2 weeks
Adalimumab (Humira®)	14 days	2 weeks
Certolizumab (Cimzia®)	14 days	2 weeks
Golimumab (Simponi®)	12±3 days	2 weeks
Infliximab (Remicade®)	8 to 9.5 days	4 weeks
Tocilizumab (RoActemra®)	8-14 days	4 weeks
Rituximab (MabThera®)	First course 2 * 500mg 15-16 days 2 * 1000mg 17-21 days Second course 2 * 500mg 19 days 2 * 1000mg 21-22 days	A minimum of 12 weeks recommended

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Department of Health Green Book Website:

<https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book>

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