North Central London
Joint Formulary Committee

Quick Reference Guide for Primary Care Prescribers

Monitoring Disease Modifying Anti-Rheumatic Drugs (DMARDs)

Azathioprine, Mercaptopurine, Sulfasalazine, Hydroxychloroquine, Ciclosporin & Penicillamine in adults

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October 2017	V4.1	Amendment to hydroxychloroquine ophthalmology monitoring made. Agreed by Camden Medicines Management Committee: October 2017
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FACTSHEET TO FACILITATE PRESCRIBING

PLEASE NOTE THIS IS NOT A SHARED CARE GUIDELINE, NOR IS IT A FULL SUMMARY OF DRUG INFORMATION. ALWAYS REFER TO THE MOST RECENT BNF AND/OR SUMMARY OF PRODUCT CHARACTERISTICS.

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NCL JFC is funded by and provides advice to Acute Trusts and Clinical Commissioning Groups in NCL.

This booklet discusses the commonly used systemic immunosuppressive drugs. It is not an alternative to using the BNF, its related appendices and any local disease specific treatment protocol or guidelines. The relevant SPC may also provide more detail on side effects and the licensing information. Drug interactions should be checked, especially for those taking, for example, warfarin, antiepileptics, antifungals, antipsychotics and digoxin.

NB: Pre-treatment screening and baseline tests are needed before initiating treatments and these will be the responsibility of the initiating prescribers in secondary care. Therefore, this booklet provides a quick reference for the safe continued prescribing in primary care, when patients have been stabilised on treatment.

Use of DMARDs for Rheumatology indications[1,2,3,4,]

Disease-modifying anti-rheumatic drugs (DMARDs) can affect the progression of rheumatic disease but may require 2–6 months of treatment for a full therapeutic response. Response to DMARDs may allow the dose of the non-steroidal anti-inflammatory drugs (NSAID) to be reduced or withdrawn.

All patients with suspected inflammatory joint disease should be assessed by a specialist as soon as possible to confirm diagnosis and evaluate disease activity; early initiation of DMARDs is recommended to control the signs and symptoms, and to limit joint damage.

The choice of a DMARD should take into account co-morbidity and patient preference.

A combination of DMARDs (including methotrexate and at least one other DMARD) and a short-term corticosteroid should be given to patients with newly diagnosed active rheumatoid arthritis, ideally within 3 months of the onset of persistent symptoms. If the use of particular DMARDs is contra-indicated and combination therapy is not possible, monotherapy with a suitable DMARD should be given and the dose rapidly increased until clinically effective. In patients with established and stable rheumatoid arthritis, cautiously reduce drug doses to the lowest that are clinically effective. Response to drug treatment often produces a reduction in requirements of both corticosteroids and other drugs.

Use of DMARDs for Gastro-intestinal indications[1,5,6,7]

Patients with acute severe ulcerative colitis not responding to oral or intravenous corticosteroids may benefit from a short course of intravenous ciclosporin (unlicensed)[7].

Patients with unresponsive or chronically active IBD may benefit from azathioprine, mercaptopurine (unlicensed) or once-weekly methotrexate (unlicensed – specialist use only). These drugs have a slower onset of action so precludes usage as sole therapy for active disease.

Use of DMARDs for Dermatology indications[8]

This guidance also includes the use of DMARDs in dermatology, although many indications are unlicensed in dermatology. Further information on use of DMARDs in dermatology for various indications can be found on the British Association of Dermatologists website and by referring to the relevant NICE and SIGN guidelines for example psoriasis. GPs may also wish to refer to the Primary Care Dermatology Website for diagnostic and management information.

Specialists should always ensure patients are stable prior to asking GPs to take over responsibility for ongoing monitoring and prescribing.

Methotrexate

Methotrexate is NOT included in this guidance. Please refer to the NCL shared care guideline for methotrexate.

Leflunomide

Leflunomide is NOT included in this guidance as it is on the NCL Red list. It is not suitable for prescribing in primary care and GPs should not be asked to take on the prescribing of Leflunomide.

Abbreviations used in this document

ALT	Alanine aminotransferase
AST	Aspartate transaminase
CRP	C reactive protein
DMARDS	Disease modifying anti-rheumatic drug
FBC	Full blood count
GFR	Glomerular flow rate
LFT	Liver function tests
MCV	Mean corpuscular volume
6-TGN	**6-thioguanine nucleotide**
TPMT	Thiopurine methyltransferase
U&E	Urea and Electrolytes
VZV	**Varicella zoster virus**
WBC	White blood cell count

<table>
<tr><th rowspan="2">DRUG</th><th colspan="3">TYPICAL DOSE[A]</th><th rowspan="2">PRE-TREATMENT</th><th rowspan="2">FBC</th><th rowspan="2">U&E & Creatinine</th><th rowspan="2">LFT & Albumin</th><th rowspan="2">DOSE ALTERATIONS / OTHER MONITORING</th></tr>
<tr><th>Gastro-Intestinal</th><th>Rheumatology</th><th>Dermatology</th></tr>
<tr><td rowspan="2">Azathioprine[B,1,2,5,8,9,10]</td><td>2-2.5 mg/kg daily
Some patients may respond to lower doses</td><td></td><td></td><td rowspan="2">Baseline TPMT status* (secondary care responsibility prior to initiating therapy)

FBC, U&E, Creatinine, LFT, albumin

Screen for hepatitis B & C, VZV serology, & HIV serology in all patients.</td><td colspan="3">Weekly for 4 weeks,
THEN monthly for 3 months.
Once stable, monitor every 3 months**</td><td>After dose alteration: repeat FBC, LFTs, U&Es, CRP and 6-TGN after 6 weeks (NB. 6-TGN is only done in secondary care. If tests results stable, return to previous schedule or as advised by gastroenterology team)</td></tr>
<tr><td></td><td>1mg/kg/day (total daily dose) increasing at 2-6 weekly intervals to maximum up to 2-3mg/kg/day</td><td><u>Unlicensed indication</u>
1mg/kg/day (total daily dose) increasing at 2-6 week intervals to maximum 3mg/kg/day
[Severe refractory eczema, immunobullous disease)] If for any other dermatological conditions, consult with specialist.</td><td colspan="3">Every 2 weeks until stable dose for 6 weeks
THEN once stable, monitor monthly for 3 months
THEN monitor every 3 months**</td><td>After dose alteration: monitor FBC, U&Es, creatinine/calculated GFR, LFT’s and albumin every 2 weeks until on stable dose for 6 weeks then revert back to previous schedule or as advised by rheumatology/dermatology team</td></tr>
<tr><td rowspan="2">Sulfasalazine[2,11,12]</td><td></td><td>Start at 500mg/day increasing by 500mg weekly to a maximum dose of 2-3g/day in divided doses.

<u>NB</u>. Only the <u>EC</u> tablets are licensed for RA</td><td rowspan="2">No dermatology indication</td><td rowspan="2">FBC, U&Es, Creatinine, LFTs, albumin,

Screen for hepatitis B & C, VZV serology, & HIV serology in all patients.</td><td colspan="3">Every 2 weeks until stable dose for 6 weeks
THEN once stable, monitor monthly for 3 months
THEN monitor every 3 months**

AFTER 12 months, no routine monitoring needed</td><td>After dose alteration: monitor FBC, U&Es, creatinine/calculated GFR, LFTs and albumin every 2 weeks until on stable dose for 6 weeks then revert back to previous schedule or as advised by rheumatology teams</td></tr>
<tr><td>1-2g four times a day. Once in remission, reduce gradually to 500mg four times a day</td><td></td><td colspan="3">Monthly for 3 months
THEN once stable for 3 months, monitor every 3 months**

After 12 months, if bloods stable, monitor every 6 months.

After 2 years, if bloods stable, no routine monitoring needed.</td><td>After dose alteration: repeat FBC, U&Es, Creatinine, LFTs after 1 month, or as advised by gastroenterology team</td></tr>
<tr><td colspan="10">*Avoid treatment if TPMT homozygous recessive or low enzyme activity. Heterozygotes with intermediate TPMT levels should receive lower treatment doses
**More frequent monitoring is appropriate in patients at higher risk of toxicity</td></tr>
</table>

DRUG	TYPICAL DOSE[A]			PRE-TREATMENT	FBC	U&E, Creatinine	LFT & Albumin	DOSE ALTERATIONS / COMMENT
	Gastro-Intestinal	Rheumatology	Dermatology					
Mercaptopurine[C5,10,13]	**Unlicensed indication** 0.75-1.5 mg/kg/day. Dose adjustments should be at 4-6 week intervals	**No rheumatology indication**	**No dermatology indication**	Baseline TPMT status* (secondary care responsibility prior to initiating therapy) FBC, U&E, Creatinine, LFT, albumin Screen for hepatitis B & C, VZV serology, & HIV serology in all patients.	**Weekly** for 4 weeks THEN monitor **monthly** for 3 months. Once stable, monitor **every 3 months**			*Avoid treatment if TPMT homozygous recessive or low enzyme activity. Heterozygotes with intermediate TPMT levels should receive lower treatment doses **After dose alteration:** repeat FBC, U&Es, Creatinine, LFTs after 1 month, or as advised by gastroenterology team
Ciclosporin[1,2,14]	**Unlicensed indication** A short course of IV **ciclosporin** may be given in 2° care for severe ulcerative colitis unresponsive to IV cortico-steroids	Starting dose of 2.5mg/kg/day in 2 divided doses equally distributed throughout the day. Increase gradually if necessary after 6 weeks to maximum 4mg/kg/day.	Starting dose of 1.25-2.5 mg/kg/day in 2 divided doses equally distributed throughout the day; increased gradually to maximum 5 mg/kg daily if no improvement within 1 month (2 weeks for atopic dermatitis). *[severe atopic dermatitis, severe psoriasis, chronic spontaneous urticaria]*	FBC, U&E, LFT, Creatinine. albumin, baseline renal function should be obtained by at least 2 readings Blood pressure and glucose Serum lipids Blood cholesterol and magnesium Screen for hepatitis B & C, VZV serology, & HIV serology in all patients.	**Every 2 weeks** until dose stable for 6 weeks THEN monitor **monthly** for at least 12 months after initiation. Continuation of ciclosporin after 12 months should only be under the care of a specialist dermatology consultant in secondary care. Most patients will stop treatment after 12 months.			Monitor BP and glucose at **every** monitoring visit If hypertension develops, appropriate antihypertensive treatment must be started. Preference should be given to an antihypertensive agent that does not interfere with the pharmacokinetics of ciclosporin **Serum lipids one month after initiating treatment** **After dose alteration –** monitor FBC, U&Es, creatinine/calculated GFR, LFTS and albumin every 2 weeks until on stable dose for 6 weeks then revert back to previous schedule or as advised by specialist
Penicillamine[15]	**No gastro-enterology indication**	Starting dose of 125-250mg/day, Increase by same amount every 4-12 weeks until remission. Usual maintenance dose of 500-750mg/day in divided doses. (Max dose 1.5g/day) [12]	**No dermatology indication**	FBC, U&E, Creatinine Urine analysis Screen for hepatitis B & C, VZV serology, & HIV serology in all patients.	**Weekly** for 8 weeks until dose stable THEN **monthly** thereafter	---	---	**Monitor urinalysis** - **Weekly** for 8 weeks until dose stable THEN **monthly** thereafter **After dose alteration:** monitor FBC and urinalysis

DRUG	TYPICAL DOSE[A]			PRE-TREATMENT	FBC	U&E, Creatinine	LFT & Albumin	DOSE ALTERATIONS / COMMENT
	Gastro-Intestinal	Rheumatology	Dermatology					
Hydroxychloroquine[2,16]	**No gastro-enterology indication**	200mg - 400mg daily. Maximum 6.5mg/kg/day. 400mg daily doses should be given in divided doses. (Should be calculated based on ideal, not actual body weight)	200mg - 400mg daily. Maximum 6.5mg/kg/day 400mg daily doses should be given in divided doses. (Should be calculated based on ideal, not actual body weight) *[Dermatological conditions caused or aggravated by sunlight]*	FBC, U&E, LFT, creatinine Within 6 months of commencing treatment, patients should have a formal ophthalmic examination, ideally including objective retinal assessment. (See Comments section). Screen for hepatitis B & C, VZV serology, & HIV serology in all patients.	No routine laboratory monitoring required. Blood counts will be done in secondary care as part of the clinical review.			Patient should immediately report any visual disturbances, including abnormal colour vision, pigmentary abnormality or visual field defects The referral to the ophthalmologist, or appropriately equipped optician, for retinal assessment is the responsibility of the initiating clinician. Some trusts do not have an in-house ophthalmology service to which a referral can be made. Negotiations are underway to implement consultant to consultant direct referral for ophthalmology assessments at another hospital. In the meantime, the GP may be requested to make the ophthalmology referral. This position will be updated in next version of this guideline. If treatment is continued for >5 years, annual eye assessments are recommended (ideally including optical coherence tomography)

Table references[1,8,13]

A. Typical dosing schedule refers to adult doses, for information on children, refer to individual Summary of Product Characteristic (SPC).
B. Dermatologists use azathioprine for many dermatological conditions. See: http://www.bad.org.uk/
C. Mercaptopurine is licensed for use in acute and chronic myeloid leukaemia. The use of oral cytotoxics for oncology indications is on the NCL 'Red List', therefore, the prescribing and supply of oral cyotoxics should remain with the specialists in secondary care. Although widely used in inflammatory bowel disease (IBD), it is not licensed for this indication and there is no agreed shared care guideline agreed for this indication. As the drug is being used 'off-label', if you are happy to continue to prescribe for IBD, it is important to ensure that the patient has been initiated and stabilised by the specialist, a clear treatment plan is in place, and monitoring requirements and guidance on toxicity are adhered to.

General notes[1,2,17,18]

1. Monitor patient's overall health and well-being.
2. Report any adverse events to the specialist team, where appropriate.
3. Report any adverse events to the MHRA via www.mhra.gov.uk/yellowcard where appropriate.
4. Help in monitoring the progression of disease.
5. Prescribe the drug treatment as recommended by specialist team.

- The summary guideline does not address combination therapy.
- Beware of drug interactions; always refer to the BNF and SPC for individual drugs before prescribing.
- Do not administer any live vaccines to these patients.
- Vaccinations against influenza and pneumococcus are recommended[2].
- Patients are more susceptible to infections, therefore check FBC, U&Es, LFTs & CRP, and treat accordingly.
- Blood disorders - patients should be advised to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise. Drug treatment should be stopped immediately if there is suspicion of a blood dyscrasia.
- Watch out for oral ulceration/sore throats/nose bleeds/bruising/rash
- If patients come into close contact with Herpes Zoster, consider passive immunisation. If necessary, seek specialist advice because testing in secondary care may be needed.[17]
- If diagnosis of stage 1 or 2 hypertension, manage hypertension according to NICE Hypertension Guidance.

Gastroenterology/Dermatology/Rheumatology Monitoring – Action to be taken[19]

Liaise with specialist in case of any of the following which may be reason to consider withdrawal or dose alteration.

Adverse effect	Action to be taken
Abnormal bruising or severe sore throat	Immediate FBC and withhold DMARD until FBC result available. *Discuss* with specialist
Severe rash or oral ulceration, unexplained illness including nausea and vomiting, diarrhoea	Withhold DMARD *until discussed* with specialist
WBC <3.5 x 10^9/l	
Neutrophils <2 x 10^9/l	
Unexplained Eosinophil >0.5 x 10^9/l	
Platelet count <150 x 10^9/l	
Significant deterioration in renal function – increase in creatinine > 30% of baseline OR decrease in calculated GFR < 60ml/min	
AST/ALT > twice upper limit of reference range	
Unexplained reduction in serum albumin <30g/L	
MCV > 105 f/l	Withhold and check serum B12, folate and TFT and discuss with specialist if necessary

As well as responding to absolute values in laboratory tests, it is also relevant to observe trends in results (e.g. gradual decreases in WBC or albumin, or climbing liver enzymes). Clinical signs should also be taken into consideration.

Contact details for specialist teams

The consultant and specialist team should ensure that their individual contact details are included within any communication letters to enable the GP to contact them for further support or advice, as needed.

Whittington Hospital	
Switchboard number:	0207 272 3070
Rheumatology CNS:	0207 288 5257
Rheumatology consultant:	0207 288 5740
Dermatology CNS:	0207 288 5062
Dermatology consultant:	0207 288 5266
Gastroenterology CNS:	TBC
Gastroenterology consultant:	TBC
North Middlesex Hospital	
Switchboard number:	0208 887 2000
Rheumatology CNS:	0208 887 3662 (Deborah Palmer)
Rheumatology consultant:	0208 887 2347 (Dr Mukerjee)
Dermatology CNS:	TBC
Dermatology consultant:	TBC
Gastroenterology CNS:	0208 887 2960
Gastroenterology consultant:	0208 887 2251 (Dr Dor)
Royal Free Hospital	
Switchboard number:	0207 794 0500
Rheumatology CNS:	Extension 32494 / 34062 or rf-tr.rheumnurseshampstead@nhs.net
Rheumatology consultant:	Extension 32494
Dermatology CNS:	Extension 31623
Dermatology consultant:	Extension 31623
Gastroenterology CNS:	0207 830 2283 or rf.ibdnurses@nhs.net
Gastroenterology consultant:	0207 830 2283
Barnet Hospital	
Switchboard number:	0208 216 4600
Rheumatology CNS:	0208 216 4523
Rheumatology consultant:	0208 216 4028 / 5470
Dermatology CNS:	0208 216 5489
Dermatology consultant:	0208 216 5489
Gastroenterology CNS:	n/a
Gastroenterology consultant:	n/a
Chase Farm Hospital	
Switchboard number:	0208 375 2999
Rheumatology CNS:	0208 375 1628
Rheumatology consultant:	0208 375 1608
Dermatology CNS:	0208 375 1999
Dermatology consultant:	0208 375 1999
Gastroenterology CNS:	n/a
Gastroenterology consultant:	n/a
University College London hospitals	
Switchboard number:	0203 456 7890
Rheumatology CNS:	0203 447 9215 / 9035 / 9281 or
Rheumatology consultant:	uclh.rheumatology@nhs.net
Dermatology CNS:	07507790466
Dermatology consultant:	uclh.dermatology@nhs.net
Gastroenterology CNS:	0203 447 5120 or
Gastroenterology consultant:	IBD.Advice@uclh.nhs.uk
St Marys Hospital	
Switchboard number:	0203 311 1234
Rheumatology CNS:	0203 312 3795
Rheumatology consultant:	Secretary – 0203 312 7789
Dermatology CNS:	0203 312 5661
Dermatology consultant:	Secretary – 0203 312 1083
Gastroenterology CNS:	n/a
Gastroenterology consultant:	Secretary – 0203 312 1208

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