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**NHS**

# Suggestions for Drug Monitoring in Adults in Primary Care

October 2017

A Collaboration between London & South East Medicines Information Service, South West Medicine Information Service and Croydon Clinical Commissioning Group.

The monitoring parameters cited are derived from a range of guideline sources, other reference sources and expert opinion and must therefore be considered suggestions only. Adherence to them will not ensure a successful outcome in every case. The ultimate judgement regarding a particular clinical result must be made by the doctor in light of the clinical data presented by the patient and the diagnostic and treatment options available.

It is intended to review and update this document again in 2019, to check if this is the latest edition visit the Specialist Pharmacy Service website at [www.sps.nhs.uk](http://www.sps.nhs.uk) alternatively contact David Erskine at London and South East Regional Medicines Information, [david.erskine@gstt.nhs.uk](mailto:david.erskine@gstt.nhs.uk)

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## ACE inhibitors and angiotensin II receptor antagonists

### Tests prior to starting treatment

- U&Es (incl urea and creatinine)<sup>1,3</sup>
- eGFR<sup>1,2</sup>
- BP<sup>1,2,3,6</sup>

See BNF for more detail regarding initiation in patients with hyponatraemia (< 130mmol/L), hypovolaemia, severe or unstable heart failure, known renovascular disease, hypotensive (SBP < 90mmHg) or taking multiple or high-dose diuretics or high-dose vasodilators.<sup>4,6</sup>

Seek further advice in patients with hypertension or eGFR < 30ml/min/1.73m<sup>2</sup> <sup>6</sup>

In patients with CKD, ACEI/ARB therapy should not normally be started if the pre-treatment serum potassium is >5.0mmol/L <sup>2,7</sup>. Similarly caution is advised in patients with heart failure<sup>8,9</sup>

### Monitoring until patient is stabilised

#### IN GENERAL

CKS advise monitoring renal function and serum electrolytes 1–2 weeks after starting treatment and 1–2 weeks after each dose increase and monitoring BP 4 weeks after each dose titration<sup>6</sup>. For people who are at higher risk of hyperkalaemia or deteriorating renal function (for example those with peripheral vascular disease, diabetes mellitus, or pre-existing renal impairment or older people), consider checking renal function and serum electrolytes within 1 week of each dose titration<sup>6</sup>

**Commented [ED1]:** Requires local decision on whether to implement common monitoring policy irrespective of indication.

#### HEART FAILURE

Measure serum urea, creatinine and electrolytes 1-2 weeks after initiation and after each dose increment. <sup>1,8</sup>

Monitor BP.<sup>1,8</sup>

#### HYPERTENSION

NICE do not provide specific advice on monitoring ACEI/ ARB therapy in hypertension except in when using further diuretic therapy for resistant hypertension at step 4, where they suggest monitor blood sodium and potassium and renal function within 1 month.<sup>3</sup>

#### CKD

Measure serum potassium concentrations and estimate the GFR between 1 and 2 weeks and after each dose increase. <sup>2</sup>

#### POST-MI

Measure renal function (serum creatinine), electrolytes and BP 1-2 weeks after initiation and after each dose increment <sup>3</sup>

## Ongoing Monitoring

**Commented [ED2]:** Requires local decision on whether to implement common monitoring policy irrespective of indication.

### HEART FAILURE

Measure serum urea, creatinine and electrolytes every 3 months and more frequently in patients taking combined loop and thiazide diuretic therapy and in those taking aldosterone antagonists.<sup>1</sup>

For other patients NICE and CKS advise that monitoring is required at least 6-monthly for stable patients with proven heart failure<sup>1,9</sup> but CKS recommend more frequent monitoring (for example every 3 months) when there are concerns regarding the person's clinical condition, concomitant drugs, or comorbidities<sup>9</sup>.

SIGN advise that in patients with cardiac failure blood urea, creatinine and electrolytes should be monitored frequently and serially until potassium and creatinine have plateaued<sup>8</sup>.

Monitor BP routinely<sup>1</sup>

### HYPERTENSION

NICE do not provide advice on monitoring ACEI/ ARB therapy in hypertension except in when using further diuretic therapy for resistant hypertension at step 4, where they suggest monitor blood sodium and potassium and renal function within 1 month and repeat as required thereafter.

CKS advise checking electrolytes and renal function regularly in stable hypertensive patients that do not have diabetes but do not provide any recommendation on frequency.<sup>6</sup>

### CHRONIC KIDNEY DISEASE (CKD)

NICE do not provide specific advice on monitoring ACEI/ ARB therapy in stable patients.

CKS advise that in patients with CKD that is not due to diabetes BP should be measured every 3–6 months, and urea and electrolytes, and eGFR, every 12 months (unless required more frequently because of impaired renal function).<sup>7</sup>

### POST-MI

Measure renal function (serum creatinine), electrolytes and BP at least annually. More frequent monitoring may be needed in patients who are at increased risk of deterioration in renal function. Patients with chronic heart failure should be monitored in line with 'Chronic heart failure' described above.<sup>3</sup>

### Action required if abnormal results

Stop ACEI/ARB therapy if serum potassium rises above 6.0mmol/L and other drugs known to promote hyperkalaemia have been discontinued.<sup>1,2, 6</sup>

If eGFR falls by 25% or more or plasma creatinine increases by 30% or more from baseline, stop the ACEI/ARB or reduce to a previously tolerated dose once potential alternative causes of renal impairment have been ruled out. If the changes indicating a

decrease in renal function are less than described do not modify the dose but repeat the test in 1-2 weeks. <sup>1,2</sup>

SIGN recommend that in patients with heart failure that if potassium rises to >5.5 mmol/l or creatinine increases by >100% or to above 310 micromol/l the ACE inhibitor should be stopped and specialist advice sought<sup>8</sup>.

If Na <132mmol/L specialist advice should be obtained<sup>5</sup>

### **Additional notes**

There are some parts of the NHS who are advising patients to temporarily stop these medicines during sick days (ie on days when they are experiencing diarrhoea or vomiting (unless minor); or fever, sweats and shaking) to prevent dehydration and thus acute kidney injury. There is some controversy over whether the benefits of this advice outweigh the risks and there is a useful interim statement from the Think Kidneys Board outlining the pros and cons of this approach <sup>10</sup>

### **References**

- 1 NICE Clinical Guideline 108 – Chronic heart failure Appendix D (2010)
2. Chronic Kidney Disease: early identification and management of chronic kidney disease in adults in primary and secondary care. NICE Clinical Guideline 73 (2014)
- 3 NICE Clinical Guideline 172 – Secondary prevention for patients in primary and secondary care following a myocardial infarction (2014)
4. BNF – accessed via Medicines Complete July 2016
5. Best Practice in primary care pathology: review J Clin Pathol 2007;60:225-234
6. CKS Guideline on hypertension (not diabetic) (2015)
- 7 CKS Guideline on chronic kidney disease (not diabetic) (2016)
- 8 SIGN Guideline 147. Management of chronic heart failure. (2016)
- 9 CKS Guideline on heart failure- chronic (2016)
- 10 Think Kidneys Board. “Sick day” guidance in patients at risk of Acute Kidney Injury: an Interim Position Statement from the Think Kidneys Board (2015)

## **Acetylcholinesterase inhibitors – donepezil, galantamine, rivastigmine**

### **Tests prior to starting treatment**

Renal function (if galantamine or rivastigmine)<sup>1</sup>  
Liver function<sup>1</sup>

### **Monitoring until patient is stabilised**

None

### **Ongoing Monitoring**

Monitor body weight (rivastigmine only)<sup>1</sup>. However both rivastigmine and galantamine can decrease appetite<sup>2</sup> so perhaps this advice should be applied to patients receiving either treatment.

### **Action required if abnormal results**

See product information for initiation of these agents in patients with impaired liver function (all three drugs) or renal function (galantamine or rivastigmine only).

Galantamine is contraindicated in people with severe renal impairment (creatinine clearance less than 9mL/min or chronic kidney disease stage 5 [estimated glomerular filtration rate < 5mL/minute/1.73m<sup>2</sup>]) or severe hepatic impairment (Child–Pugh score greater than 9)<sup>2</sup>

### **Additional notes**

Specialist initiation only but may be continued and monitored by the GP under a shared care protocol.<sup>1,2</sup>

Monitor patient for side effects, most commonly presenting as cholinergic effects. The specialist should be contacted in the event of intolerance or adverse events to the medication. The specialist should also be contacted if there is sudden deterioration in cognitive function<sup>2</sup>.

Patients prescribed galantamine should be warned of the signs of serious skin reactions and advised to stop taking galantamine immediately and seek medical advice should such symptoms occur<sup>1</sup>

### **References**

1. BNF – accessed via Medicines Complete July 2016
2. Clinical Knowledge Summary. Dementia. Last revised April 2015

## **Amiodarone**

### **Tests prior to starting treatment**

Treatment should normally be initiated and monitored under hospital or specialist supervision<sup>1</sup>

TFTs (FT4, FT3 and TSH)

A UK guideline on TFTs also recommends measuring thyroid peroxidase antibodies (TPOAb) to assess risk for thyroid dysfunction,<sup>3</sup>

LFTs (particularly transaminases)<sup>1,4,5</sup>

U&Es<sup>4,5</sup>

ECG and potassium level<sup>1,4,5</sup>

Chest X-ray<sup>1,2,4,5</sup>

### **Monitoring until patient is stabilised**

In warfarinised patients, more frequent monitoring of INR both during and after amiodarone treatment is recommended<sup>1</sup>; initially weekly for first 7 weeks<sup>5</sup>

### **Ongoing monitoring**

TFTs every 6 months<sup>1-5</sup> and for some months after discontinuation<sup>1</sup> (UK guideline on TFTs suggests up to 12 months after cessation<sup>3</sup>)

Serum TSH should also be measured when thyroid dysfunction is suspected.<sup>1</sup>

LFTs every 6 months<sup>1,4,5</sup>

U&Es every 6 months<sup>4,5</sup>

Chest X-ray every 12 months<sup>4,5</sup>

ECG every 12 months<sup>4,5</sup>

Unless blurred or decreased vision occurs, ophthalmological examination is recommended annually<sup>1</sup>, although the DTB states that these are usually only necessary for patients with visual symptoms<sup>6</sup>

### **Action required if abnormal results**

If TFTs are borderline repeat test in 6 weeks<sup>7</sup>

Amiodarone may cause isolated biochemical changes (increase free-T4, slight decrease/normal free-T3) in clinically euthyroid patients, but there is no reason in such cases to discontinue amiodarone if there is no clinical or further biological (TSH) evidence of thyroid disease.<sup>1</sup>

Amiodarone-associated hyperthyroidism should be diagnosed only if high circulating free T4 is associated with high or high/normal free T3 and undetectable TSH<sup>3</sup>; such a diagnosis should prompt withdrawal of amiodarone<sup>1</sup> and specialist referral.<sup>3</sup> Clinical recovery usually occurs within a few months of drug withdrawal, although severe

cases, sometimes resulting in fatalities, have been reported. Clinical recovery precedes normalisation of TFTs.<sup>1</sup>

Diagnosis of hypothyroidism following development of symptoms is supported by increase in TSH and an exaggerated TSH response to TRH; also T3 and T4 levels may be low. Euthyroidism is usually obtained within 3 months following discontinuation of treatment. In life-threatening situations, amiodarone therapy can be continued, in combination with levothyroxine.<sup>1</sup>

Treatment should be discontinued if severe liver function abnormalities or clinical signs of liver disease develop<sup>2</sup>

If blurred or decreased vision occurs, complete ophthalmologic examination including fundoscopy should be promptly performed.<sup>1</sup>  
Appearance of optic neuropathy and/or optic neuritis requires amiodarone withdrawal due to the potential progression to blindness<sup>1</sup> and expert opinion sought<sup>2</sup>

If pulmonary toxicity is suspected, chest X ray should be repeated and lung function tested, including where possible, measurement of transfer factor.<sup>1</sup> Specialist referral advised.<sup>6</sup>

Pneumonitis should always be suspected if new or progressive shortness of breath or cough develops in a patient taking amiodarone<sup>2</sup>

#### **Additional notes**

Most patients on amiodarone develop corneal microdeposits (reversible on withdrawal of treatment) which rarely interfere with vision but drivers may be dazzled by headlights at night.<sup>2</sup>

Fresh neurological symptoms should always raise the issue of peripheral neuropathy<sup>2</sup>

Patients should be advised to shield skin from light during treatment and for several months after discontinuing amiodarone and to use a wide-spectrum sunscreen to protect against both long UV and visible light<sup>2</sup>

Because of long half-life of amiodarone, clinical problems may occur up to a year after stopping the drug<sup>3</sup> (hyperthyroidism may occur up to several months after discontinuation<sup>1</sup>).

Measurement of free T3 is required for interpreting results when free T4 or TSH values are outside reference limits, and it is important that information about drugs taken is available to laboratory so that correct thyroid tests can be selected and erroneous interpretation avoided.<sup>4</sup>

TPOAb are present in serum of patients with wide range of immunologically mediated thyroid disorders and may also be found in a small proportion of apparently healthy individuals; their appearance usually precedes development of thyroid disorders<sup>3</sup>

## References

1. Summary of Product Characteristics for Cordarone 100mg and 200mg Tablets. SPC (date of revision Mar 2016)
2. BNF – accessed via Medicines Complete July 2016
3. Association for Clinical Biochemistry (ACB), the British Thyroid Association (BTA) and the British Thyroid Foundation (BTF). UK Guidelines for the Use of Thyroid Function Tests July 2006. [http://www.british-thyroid-association.org/info-for-patients/Docs/TFT\\_guideline\\_final\\_version\\_July\\_2006.pdf](http://www.british-thyroid-association.org/info-for-patients/Docs/TFT_guideline_final_version_July_2006.pdf)
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5. Smellie WSA, Forth J, Sundar S, et al. Best practice in primary care pathology: review 4. *J Clin Pathol.* 2006 September; 59(9): 893–902. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1860479/>
6. Anon: Using oral amiodarone safely. *DTB* 2003 41: 9-12. <http://dtb.bmj.com/content/41/2/9.full.pdf+html>
7. Newman CM, Price A, Davies DW, et al. Amiodarone and the thyroid: a practical guide to the management of thyroid dysfunction induced by amiodarone therapy. *Heart* 1998;79:121–127. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1728611/pdf/v079p00121.pdf>

## Antipsychotic agents

### Tests prior to starting treatment

FPG<sup>2,5,6</sup> (NICE state either FPG or HbA1c in bipolar disorder is acceptable<sup>3</sup>, SLAM state that although fasting plasma glucose is preferable, random plasma glucose is acceptable<sup>1</sup>)

HbA1c<sup>2,3,5</sup> (NICE state either FPG or HbA1c in bipolar disorder is acceptable<sup>3</sup>)

BP<sup>1,2,3,5,6</sup>

Pulse<sup>2,3,5</sup>

FBC<sup>5</sup>

LFTs<sup>1,5</sup>

U&Es<sup>1,4,5</sup>

Blood lipid profile<sup>1,2,3,5,6</sup> (SLAM state that although fasting sample is preferable a non-fasting sample is acceptable<sup>1</sup>)

CPK<sup>1</sup>

Smoking history<sup>5,6</sup>

Weight (include waist circumference)<sup>1,2,3,5,6</sup>

BMI<sup>1,3,4,6</sup>

NICE also advise an assessment of nutritional status, diet and level of physical activity<sup>2</sup>

The BNF states that patients with schizophrenia should have physical health monitoring (including cardiovascular disease risk assessment) at least once per year<sup>4</sup>

Prolactin<sup>1,2,3,4,5</sup> –CKS recommend only for quetiapine or olanzapine<sup>5</sup> and SIGN recommends only if clinically indicated.<sup>6</sup> NICE suggest when used in schizophrenia but not in bipolar disorder<sup>2,3</sup>

ECG<sup>1,2,3,4</sup> - NICE/SIGN recommends if clinically indicated or recommended in SPC for that product.<sup>2,3,6</sup> CKS states only required if the person is taking haloperidol, pimozide or sertindole if they have had a previous ECG abnormality, or if they have an additional risk factor for QT prolongation (for example taking another medication that can increase the QT interval such as erythromycin, co-trimoxazole, or pregabalin)<sup>5</sup>.

### Monitoring until patient is stabilised

BP: in schizophrenia NICE recommend monitoring at 12 weeks in schizophrenia.<sup>2</sup> and after each dose change in bipolar disorder<sup>3</sup>

Other guidelines recommend frequent checks during dose titration phase<sup>1,4,5</sup> or at 1 month (if clinically indicated) and 3 months.<sup>6</sup>

Pulse: NICE recommend monitoring at 12 weeks in schizophrenia.<sup>2</sup> and after each dose change in bipolar disorder<sup>3</sup>

FPG: NICE recommend monitoring at 12 weeks<sup>2,3</sup>. Other guidelines recommend checking after 1 month then every 4-6 months<sup>5</sup> or at 1 month (if clinically indicated)

**Commented [ED3]:** Local decision needed on whether to adhere to NICE recommendation or accept random plasma glucose levels as adequate for some patients.

and 3 months<sup>3,6</sup> (and more often if elevated)<sup>3</sup>. SLAM state that although fasting plasma glucose is preferable, random plasma glucose is acceptable<sup>1</sup>

HbA1c: NICE recommend monitoring after 12 weeks.<sup>2,3</sup>

Weight: In schizophrenia NICE recommend weekly for first 6 weeks and then at 12 weeks and 1 year plotted on a chart.<sup>2</sup> Other guidelines recommend every 3 months for 1st year<sup>1,4,5</sup>, or at 1 month (if clinically indicated) and 3 months<sup>6</sup>

Lipids: In schizophrenia NICE recommend assessment at 12 weeks<sup>2,3</sup>. Other guidelines recommend every 3 months for first year<sup>1,3,4,5</sup>, or at 1 month (if clinically indicated) and 3 months<sup>6</sup> (or more often if weight gain is rapid)<sup>3</sup>.

ECG: After each dose change<sup>1,5</sup> or if clinically indicated<sup>6</sup>

Prolactin: At 6 months<sup>1,4,5</sup> and if clinically indicated<sup>4,6</sup>

Smoking history at 3 months<sup>6</sup>

### Ongoing monitoring

Every 12 months: FBC, U&Es, LFTs, weight, lipids, prolactin, BP, FPG.<sup>1,5,6</sup> NICE only recommend measurement of weight, waist circumference, BP, pulse, and HbA1c and fasting blood glucose every 12 months in patients being treated for schizophrenia<sup>2</sup>. SLAM state that although fasting plasma glucose is preferable, random plasma glucose is acceptable<sup>1</sup>

The BNF states that patients with schizophrenia should have physical health monitoring (including cardiovascular disease risk assessment) at least once per year<sup>4</sup>

Other guideline producers recommend FPG measurements every 4-6 months.<sup>1,4,5</sup> With increased clinical monitoring of signs and symptoms of hyperglycaemia and worsening of glucose control in patients with diabetes or at risk of developing diabetes mellitus.<sup>2</sup>

CPK if neuroleptic malignant syndrome (NMS) suspected<sup>1</sup>

ECG: after each dose change<sup>1,5</sup> or if clinically indicated<sup>6</sup>- CKS states only required if the person is taking haloperidol, pimozide or sertindole if they have had a previous ECG abnormality, or if they have an additional risk factor for QT prolongation (for example taking another medication that can increase the QT interval such as erythromycin, co-trimoxazole, or pregabalin)<sup>5</sup>.

Smoking history<sup>6</sup>

### Action required if abnormal results

If blood lipids outside range, offer lifestyle advice or consider changing antipsychotic and/or initiating statin therapy.<sup>1</sup>

**Commented [ED4]:** Local decision needed on whether to adhere to NICE recommendation or accept random plasma glucose levels as adequate for some patients

If weight outside range, offer lifestyle advice. Consider changing antipsychotic and/or dietary/pharmacological intervention. <sup>1</sup>

If hyperprolactinaemia confirmed and symptomatic, switch drugs. <sup>1</sup>  
If NMS suspected, stop therapy<sup>1</sup>

If LFTs indicate hepatitis (transaminases x3 normal) or functional damage (PT or albumin change), stop therapy<sup>1</sup>

### **Additional notes**

In schizophrenia NICE advise that the secondary care team should maintain responsibility for monitoring service users' physical health and the effects of antipsychotic medication for at least the first 12 months or until the person's condition has stabilised, whichever is longer.<sup>2</sup>  
NICE recommend a regular and systematic assessment of overall physical health and adherence whilst on treatment.<sup>2</sup>

Patients with schizophrenia should have physical health monitoring (including cardiovascular disease assessment) at least once per year. <sup>4,6</sup>

When one or more factors present that might result in slower metabolism (eg female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase.<sup>4</sup>

Dose adjustment may be necessary if smoking started or stopped during treatment. <sup>4</sup>

Patients should be monitored for 2 years after withdrawal for signs and symptoms of relapse. <sup>4</sup>

### **References**

1. The South London and Maudsley NHS Trust, Oxleas NHS Trust 2015 Prescribing Guidelines 12th edition
2. NICE Guideline: Psychosis and schizophrenia in adults: treatment and management. Issued February 2014
3. NICE Guideline on the management of bipolar disorder in adults, children and adolescents in primary and secondary care. Issued Sept 2014
4. BNF – accessed via Medicines Complete Aug 2016
5. Clinical Knowledge Summaries: Schizophrenia. Last revised Feb 2015
6. SIGN 131: Management of schizophrenia. March 2013

## Apixaban

### Tests prior to starting treatment

Renal function<sup>1-3,6,7</sup>

Body weight<sup>1,2</sup>

Baseline clotting screen<sup>7</sup>

Full blood count<sup>3,7</sup>

LFTs<sup>2,3,7</sup>

BP<sup>4</sup>

**Commented [ED5]:** Renal function should be based on Cockcroft Gault calculation – a local protocol on guidance in extremes of body weight is advisable. SE London Guidance is available: <http://www.lambethccg.nhs.uk/news-and-publications/meeting-papers/south-east-london-area-prescribing-committee/Documents/Cardiovascular%20Disease%20Guidelines/Creatinine%20clearance%20guidance%20July%202017.pdf>

### Monitoring until patient is stabilised

No routine anticoagulation monitoring is needed<sup>1-3,5</sup>.

First follow-up appointment should be after 1 month<sup>3</sup>, then ideally assess patient every 3 months to<sup>3,7</sup>:

- Assess compliance and reinforce advice regarding regular dosing schedule
- Enquire about adverse effects such as bleeding
- Assess for the presence of thromboembolic events
- Enquire about other medicines, including OTC medicines

**Commented [ED6]:** Needed in conjunction with renal and liver function if want to calculate HAS-BLED score

### Ongoing monitoring

No routine anticoagulation monitoring is needed<sup>1-3,5</sup>.

Patient compliance should be assessed every three months ideally<sup>3,7</sup>.

Enquire about presence of any adverse effects, in particular signs and symptoms of bleeding and anaemia, every three months ideally<sup>1-3,7</sup>.

Renal function may decline whilst on treatment so it should be monitored annually if CrCl > 60 mL/min, every 6 months if CrCl 30-60 mL/min or every 3 months if CrCl 15-30 mL/min<sup>3,7</sup>.

The EHRA guidance suggests retesting every x-months (where  $x = \text{CrCl}/10$ ) [e.g. if CrCl 30 mL/min every 3 months, if CrCl 20 mL/min every 2 months]<sup>3</sup>.

LFTs annually<sup>3,7</sup>.

CrCl and LFTs should be performed more often if there is an intercurrent illness that may impact renal or hepatic function<sup>7</sup>.

Full blood count annually<sup>3,7</sup>.

**Commented [ED7]:** See comment above regarding estimate of renal function

### Action required if abnormal results

If CrCl < 15 mL/min stop apixaban, assess for bleeding and seek advice regarding alternative anticoagulation therapy<sup>1,2,7</sup>.

If CrCl is 15–29 mL/min, the following recommendations apply:

- For prophylaxis of recurrent DVT or PE, and treatment of DVT or PE, use apixaban with caution<sup>1,2,7</sup>.
- For prophylaxis of stroke and systemic embolism in a person with AF, reduce the dose to 2.5 mg twice daily if CrCl is 15–29 mL/minute, or if serum creatinine is 133 micromol/litre or greater and the person is 80 years of age or older or weighs 60 kg or less<sup>1,2,7</sup>.

If liver enzymes are elevated (ALT/AST > 2 x ULN or total bilirubin ≥ 1.5 x ULN) apixaban should be used with caution (these patients were excluded from clinical trials)<sup>2</sup>.

If the patient's HASBLED score is more than 3, then the patient is at a high risk of bleeding and apixaban should be used cautiously, with regular reviews<sup>4</sup>.

A low haemoglobin may suggest that occult bleeding is occurring and may require further investigations<sup>3</sup>.

#### **Additional notes**

Recently issued guidance from UKCPA recommends that apixaban should be stopped at least 2 days (ie 2 doses) before a procedure with a low bleeding risk and at least 3 days (ie 4 doses) before a procedure with a high bleeding risk. Longer periods are recommended in patients with impaired renal function. No apixaban should be taken on the day of the procedure.<sup>8</sup>

Apixaban can go into a monitored dosage system (MDS) as it does not require any special precautions for storage<sup>2</sup>.

#### **Significant drug interactions**

- Analgesics (intravenous diclofenac, ketorolac)<sup>1,2</sup>
- Antibacterials (clarithromycin, telithromycin, rifampicin)<sup>1,2</sup>
- Anticoagulants<sup>1,2</sup>, Antiplatelets<sup>2</sup>
- Antiepileptics (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone)<sup>1,2</sup>
- Antifungals (ketoconazole, itraconazole, posaconazole and voriconazole)<sup>1,2</sup>
- St John's Wort<sup>2</sup>

#### **References**

1. British National Formulary. Accessed via: <http://www.medicinescomplete.com> on 18/08/2016.
2. Eliquis. Summary of Product Characteristics for Apixaban 5mg Tablets. Last updated on the eMC 22/01/2016. Accessed via: [www.emc.medicines.org.uk](http://www.emc.medicines.org.uk) on 18/08/2016.
3. Heidbuchel H, et al, **2015**. Updated European Heart Rhythm Association practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace Advance Access published August 31, 2015. Accessed via <http://europace.oxfordjournals.org/content/europace/early/2015/08/29/europace.euw309.full.pdf> on 16/09/16.
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5. Kirchof P, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace Aug 2016, euw295; DOI: 10.1093/europace/euw295
6. MHRA: The new oral anticoagulants Eliquis®▼, Pradaxa®, Xarelto®▼ Beware of the risk factors for bleeding, pay attention to posology, contraindications, and warnings and precautions for use to reduce the risk of bleeding (September 2013). Accessed via:

- <http://www.mhra.gov.uk/home/groups/plp/documents/drugsafetymessage/con321961.pdf> on 18/08/2016.
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8. UKCPA Handbook of per-operative medicines. Published Oct 2016

## Azathioprine

### Tests prior to starting treatment

BSR recommend that all patients starting DMARDs should have baseline measurement of height, weight and BP<sup>1</sup>

FBC

Renal profile (creatinine/calculated GFR)<sup>1</sup>

Serum albumin<sup>1</sup>

ALT and/or AST<sup>1</sup>

TPMT assay<sup>1,2,5,7</sup>

There is a strong rationale for screening for hepatitis B and C in patients at increased risk of infection<sup>1,5,6</sup>

Baseline HIV status should also be established in those with risk factors<sup>1,4</sup>.

Screening for lung disease should be undertaken at clinical discretion on a case-by-case basis.<sup>1</sup>

### Monitoring until patient is stabilised

IN GENERAL

BNF recommends weekly FBC monitoring for 4 weeks (more frequently if higher doses or if hepatic or renal impairment)<sup>2</sup>

IN RHEUMATOLOGY

FBC, creatinine/calculated GFR, ALT and/or AST, albumin every two weeks until dose stable for at least 6 weeks then monthly thereafter for 3 months. More frequent monitoring may be required in high-risk patients.<sup>1</sup>

Following a change in dose repeat FBC ALT and/or AST, creatinine/calculated GFR and albumin every 2 weeks until dose stable for 6 weeks and then revert to previous schedule<sup>1</sup>

IN DERMATOLOGY

FBC and LFTs weekly until stable on maintenance dose. Otherwise same as for rheumatology<sup>4</sup>

IN GASTROENTEROLOGY

BSG state that there is no evidence to support weekly monitoring as described above. FBC every 2-4 weeks for 2 months and then every 4-8 weeks is considered fairly common practice<sup>3</sup>

CKS recommends FBC every 2-4 weeks for 2 months and LFTs every week for 6 weeks then every 2 weeks until dose is stable for 6 weeks.<sup>1</sup>

GI specialists from Guys & St Thomas NHS Foundation Trust suggest monitoring FBC and LFTs at weeks 2, 4, 8 and 12.<sup>8</sup>

They also recommend that the methylmercaptopurine to thioguanine ratio (MeMP:TGN) is measured at Week 4 and 16 (and at Week 4 after each dose change).

**Commented [d8]:** Local decision needed on whether thiopurine methyltransferase (TPMT) activity result must be available before treatment with azathioprine is initiated.

The BNF (and thus NICE) advise that patients with absent TPMT activity should not receive thiopurine drugs; those with reduced TPMT activity may be treated under specialist supervision.

BAD advises that TPMT activity be checked in all patients prior to receiving azathioprine. Those with intermediate (heterozygous) range activity should receive a lower maintenance dose and those with absent activity should in general not be prescribed azathioprine. TPMT genotyping is only required for patients with indeterminate phenotype (i.e. borderline values) or those who have had a recent blood transfusion<sup>4</sup>.

BSR note that in situations where TPMT testing is not available it would be reasonable to increase laboratory monitoring to weekly in the initiation phase of treatment.

BSG state that the precise role of measuring TPMT levels in starting azathioprine / mercaptopurine therapy is still controversial.

**Commented [d9]:** NICE advise that patients taking azathioprine should be monitored according to recommendations in the BNF

**Commented [ED10]:** It is unclear if this test is routinely available or used.

## Ongoing monitoring

### IN GENERAL

BNF recommends a minimum of 3-monthly FBC monitoring and note that Blood tests and monitoring for signs of myelosuppression are essential in long-term treatment<sup>2</sup>.

**Commented [d11]:** Local decision needed on whether to follow disease specific guidance as listed or follow BNF advice

CKS recommend monitoring FBC every 4 to 8 weeks, LFTs every month but once stable for 6 months consider reducing to 3-monthly and U&Es (incl creatinine) every 6 months.<sup>1</sup>

### IN RHEUMATOLOGY

Once the maintenance dose has been achieved and stable for 3 months consider monitoring FBC, creatinine/calculated GFR, albumin, ALT and/or AST at least every 12 weeks

More frequent monitoring is appropriate in patients at higher risk of toxicity.

### IN DERMATOLOGY

No specific guidance offered<sup>4</sup>

### IN GASTROENTEROLGY

BSG suggest monitoring FBC every 4 to 8 weeks<sup>3</sup>

GI specialists from Guys & St Thomas NHS Foundation Trust suggest monitoring FBC and LFTs every 3 months and that the methylmercaptapurine to thioguanine ratio (MeMP:TGN) is measured annually.

**Commented [ED12]:** It is unclear if this test is routinely available or used

## Action required if abnormal results

Withhold treatment until discussion with consultant specialist if<sup>1</sup>:

- WCC < 3.5 x 10<sup>9</sup>/L,
- Neutrophils < 1.6 x 10<sup>9</sup>/L
- Unexplained eosinophilia > 0.5x 10<sup>9</sup>/L
- Platelets < 140x 10<sup>9</sup>/L,
- AST and/or ALT increase to >100units/L
- Unexplained fall in serum albumin <30g/L
- MCV > 105f/L
- Creatinine increase > 30% above baseline over 12 months and/or calculated GFR < 60ml/min/1.73m<sup>2</sup>

If patient develops renal impairment (eGFR < 50ml/min) check dosing with specialist

## Additional notes

Pneumococcal vaccine and annual flu vaccine should be given <sup>1,4</sup>, but live vaccines should be avoided although it is noted that the JCVI green book addresses this, recommending that low dose corticosteroids (prednisolone <20mg daily) and oral DMARD therapy at standard doses are not a contraindication in most patients, although clinician discretion is advised <sup>1</sup>.

Patients should be advised to seek urgent medical attention if they develop signs or symptoms of azathioprine hypersensitivity, bone marrow suppression or liver impairment; specifically high fever/severe flu-like illness, unexplained bleeding or bruising, or new onset jaundice<sup>2,4</sup>.

Sunscreens and protective clothing should be encouraged to reduce sunlight exposure<sup>4</sup>

Azathioprine should be temporarily discontinued until the patient has recovered from the infection<sup>1</sup>

## References

1. BSR and BHPR non-biologic DMARD guidelines (2017).
2. BNF accessed via Medicines Complete July 2017
3. BSG Guidelines for the management of inflammatory bowel disease in adults (2011) – Gut 2011; 60: 571-607,
4. British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011
5. NICE clinical guideline 152 (2012 – updated May 2016) Crohn's disease: management in adults, children and young people
6. NICE public health guidance 43 (2012): Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection
7. NICE clinical guideline 166 (2013) Ulcerative colitis management.
8. A practical guide to thiopurine prescribing and monitoring in IBD. Frontline Gastroenterology 2016;0:1–6. doi:10.1136/flgastro-2016-100738. Available: <http://fg.bmj.com/content/flgastro/early/2016/08/29/flgastro-2016-100738.full.pdf>

## **Carbimazole**

### **Tests prior to starting treatment**

TFTs (FT3 and TSH): All patients with hyperthyroidism should be referred to a specialist at diagnosis to establish the diagnosis and optimal management plan<sup>1,2</sup>  
WBC<sup>3,6</sup>  
LFTs<sup>5,6</sup>

### **Monitoring until patient is stabilised**

UK Guidelines recommended TFTs (TSH and FT4) every 4-6 weeks after initiation. The frequency should be reduced to approximately every 3 months once a maintenance dose is achieved<sup>2,6</sup>.

### **Ongoing monitoring**

UK Guidelines recommend annual TFT monitoring once stable if being used as a long-term treatment option.<sup>2</sup> CKS recommend TFT monitoring every 6 months if carbimazole is being used as part of a block and replace regimen<sup>6</sup>

Following the onset of any signs and symptoms of hepatic disorder, stop carbimazole and perform liver function tests immediately.<sup>5</sup>

### **Action required if abnormal results**

Carbimazole should not be used in patients with severe hepatic insufficiency and with caution in patients with mild to moderate insufficiency<sup>5</sup>

CSM warning (neutropenia and agranulocytosis) – patient should be asked to report symptoms and signs suggestive of infection, especially sore throat, a WBC should be performed if there is any clinical evidence of infection, carbimazole should be stopped promptly if there is clinical or laboratory evidence of neutropenia<sup>4</sup>

Repeat WBC if patient develops fever, mouth ulcers, sore throat or other symptoms of infection<sup>4</sup>

Stop drug and recommend immediate specialist referral if leucocyte count falls to  $<1500 \times 10^6/L$  or neutrophil count to  $<500 \times 10^6/L$ <sup>3</sup>

Refer to specialist endocrinologist if FT4 level falls below reference range or TSH is raised<sup>6</sup>

### **Additional notes**

Warn patient or carers to tell doctor immediately if sore throat, mouth ulcers, bruising, fever, malaise, or non-specific illness develops<sup>4</sup>

Regular full blood count checks should be carried out in patients who may be confused or have a poor memory.<sup>5</sup>

Rashes and pruritus are common with carbimazole but they can be treated with antihistamines without discontinuing therapy; alternatively propylthiouracil can be substituted<sup>4</sup>

### References

1. Consensus statement for good practice and audit measures in management of hypothyroidism & hyperthyroidism BMJ 1996;313:539-544
2. UK Guidelines for thyroid function tests by Assoc. Clinical Biochemistry, British Thyroid Assoc and British Thyroid Foundation (Jul 2006)
3. Best practice in primary care pathology: review 4. J Clin Pathol 2006; 59: 893-902
4. BNF. Accessed via Medicines Complete Nov 2016
5. SPC for carbimazole 20 mg tablets (Lime Pharma). Last revised Aug 2016
6. CKS. Hyperthyroidism. Last updated Jun 2016 (accessed via <https://cks.nice.org.uk/hyperthyroidism#!topicsummary> )

## Ciclosporin (Neoral)

### Tests prior to starting treatment

#### IN GENERAL

BP (BNF recommends two measurements before starting treatment)<sup>2</sup>  
Renal function (BNF recommends two measurements before starting treatment)<sup>2</sup>  
Liver function<sup>2</sup>  
Serum potassium<sup>2</sup>  
Serum magnesium<sup>2</sup>  
Blood lipids<sup>2</sup>

Consider NICE recommendations regarding screening for hepatitis B and C in patients at increased risk of infection<sup>1,6</sup>

Baseline HIV status should also be established in those with risk factors<sup>1,6</sup>.

#### IN RHEUMATOLOGY

BSR recommend that all patients starting DMARDs should have baseline measurement of the following:

height and weight<sup>1</sup>  
Calculated GFR or serum creatinine<sup>1</sup>  
Serum albumin<sup>1</sup>  
ALT and/or AST<sup>1</sup>  
Glucose level<sup>1</sup>

**Commented [ED13]:** Local decision on whether to use more specific recommendations for assessment of renal and liver function

### Monitoring until patient is stabilised

#### IN GENERAL

BNF recommends monitoring:

Liver function (frequency unspecified)  
Serum potassium, especially in renal dysfunction (frequency unspecified)  
Serum magnesium (frequency unspecified)  
Measure blood lipids after the first month of treatment.  
Serum creatinine every 2 weeks for first 3 months then every month  
Blood pressure (frequency unspecified)

#### IN RHEUMATOLOGY

FBC  
creatinine/calculated GFR  
ALT and/or AST  
Albumin

All measured every two weeks until dose stable for at least 6 weeks then monthly thereafter for 3 months. More frequent monitoring may be required in high-risk patients.<sup>1</sup>

Following a change in dose repeat FBC, ALT and/or AST, creatinine/calculated GFR and albumin every 2 weeks until dose stable for 6 weeks and then revert to previous schedule<sup>1</sup>

BP and glucose should be checked at each monitoring visit

#### IN GASTROENTEROLOGY

BP, FBC, renal function and ciclosporin level (aim for 100-200ng/ml) at weeks 1 and 2 then monthly<sup>4</sup>

#### IN TRANSPLANTATION

No specific guidance identified

### **Ongoing Monitoring**

#### IN GENERAL

BNF recommends monitoring

Liver function (especially if concomitant NSAIDs - frequency unspecified)

Serum potassium, especially in renal dysfunction (frequency unspecified)

Serum magnesium (frequency unspecified)

Serum creatinine every month

Blood pressure (frequency unspecified)

CKS also advises that fasting lipids should be checked periodically<sup>3</sup>

#### IN RHEUMATOLOGY

##### FBC

creatinine/calculated GFR

ALT and/or AST

Albumin

All measured every month – in patients who have been stable for 12 months consider a reduced frequency on an individual patient basis.

BP and glucose should be checked at each monitoring visit

#### IN GASTROENTEROLOGY

BP, FBC, renal function and ciclosporin level (aim for 100-200ng/ml) every month

#### IN TRANSPLANTATION

No specific guidance identified

### **Action required if abnormal results**

Withhold treatment until discussion with consultant specialist if<sup>1</sup>:

- WCC < 3.5 x 10<sup>9</sup>/L,
- Neutrophils < 1.6 x 10<sup>9</sup>/L
- Unexplained eosinophilia > 0.5x 10<sup>9</sup>/L
- Platelets < 140 x 10<sup>9</sup>/l,
- AST and/or ALT-increase to >100units/ml
- Unexplained fall in serum albumin <30g/L
- MCV > 105f/L
- Creatinine increase > 30% above baseline over 12 months and/or calculated GFR <60ml/min/1.73m<sup>2</sup>

BNF advises that ciclosporin should be discontinued in patients that develop hypertension that cannot be controlled with antihypertensives<sup>2</sup>. CKS defines high BP as < 140/90 on two consecutive occasions two weeks apart<sup>3</sup>

CKS note that ciclosporin can cause a significant increase in fasting lipids<sup>3</sup>. BSG state that the risk of seizures with ciclosporin is increased in patients with a low cholesterol (<3.0 mmol/L) or magnesium (<0.5mmol/L)<sup>4</sup>

CKS advise that if patient shows signs of abnormal bruising a full blood count should be checked immediately and the drug withheld until discussed with the specialist team<sup>3</sup>

#### **Additional notes**

Oral capsule formulations may contain significant amounts of ethanol.<sup>5</sup>

Avoid excessive exposure to UV light, including sunlight<sup>2</sup>

Prescribing and dispensing of ciclosporin should be by brand name to avoid inadvertent switching. If it is necessary to switch a patient to a different brand, the patient should be monitored closely for changes in ciclosporin level, serum creatinine, BP (and transplant function where applicable)<sup>2</sup>. Switching should be made with caution and under specialist supervision<sup>5</sup>.

#### **References**

1. BSR and BHPR guideline for prescription and monitoring of non-biologic disease-disease-modifying anti-rheumatic drugs (2017)
2. BNF accessed via Medicines Complete – last updated July 2017
3. Clinical Knowledge Service Guidance – DMARDs – ciclosporin scenario (Jul 2015)
4. BSG Guidelines for the management of inflammatory bowel disease in adults – Gut 2011,
5. Summary of Product Characteristics for Neoral Soft Gelatin Capsules, Neoral Oral Solution. Date of revision of the text Jul 2015
6. NICE public health guidance 43: Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (2012 – last updated Mar 2013)

## Corticosteroids (long term oral therapy)

### Tests prior to starting treatment

Blood pressure<sup>1,2</sup>  
Body weight<sup>1,2</sup>  
BMI<sup>2</sup>  
Height (children and adolescents)<sup>1,2</sup>  
Optometrist examination for glaucoma and cataract<sup>1</sup>  
HbA1c<sup>1</sup> or fasting glucose level<sup>2</sup>  
Triglycerides<sup>1,2</sup>  
Potassium<sup>1</sup>

Assess for risk factors or pre-existing conditions that may potentially be exacerbated by steroid therapy, such as diabetes, dyslipidaemia, CVD, GI disorders, affective disorders, or osteoporosis<sup>2</sup>

Assess fragility fracture risk for all patients aged over 40 years who are currently taking or are frequent users of oral corticosteroids and all patients aged under 40 years who are current or recent users of high-dose oral corticosteroids for more than 3 months (high-dose defined as  $\geq 7.5$ mg prednisolone daily or equivalent).<sup>1</sup>

Conversely SIGN recommend that all patients taking oral corticosteroids should be considered for a fracture risk assessment and that fracture-risk assessment should be carried out, preferably using Qfracture, prior to DXA in patients with clinical risk factors for osteoporosis and in whom antiosteoporosis treatment is being considered<sup>3</sup>

**Commented [d14]:** Local decision needed on which approach preferred locally

### Monitoring until patient is stabilised

HbA1c, triglycerides and potassium — check 1 month after start of therapy<sup>1</sup>  
Check for new onset of diabetes 1 month after start of therapy<sup>1</sup>

### Ongoing monitoring

Blood pressure — monitor at every appointment<sup>1</sup>  
Triglycerides every 6–12 months<sup>1</sup>  
Potassium every 6–12 months<sup>1</sup>  
HbA<sub>1c</sub> every 3 months - monitor people with confirmed diabetes more closely<sup>1</sup>  
Body weight — monitor regularly<sup>1</sup>  
Record height of children and adolescents regularly and plot on a growth chart.<sup>1</sup>  
Perform a falls risk assessment, where appropriate, and advise those at increased risk of fractures.<sup>1</sup>

Monitor for signs of adrenal suppression.<sup>1</sup>

Eye exam every 6- 12 months; but earlier for those with symptoms of cataracts; early referral for intraocular pressure assessment if: personal/family history open angle glaucoma, diabetes, high myopia, connective tissue disease (particularly rheumatoid arthritis)<sup>1,2</sup>

### **Action required if abnormal results**

Offer weight management advice if necessary.<sup>1</sup>

Treat elevated BP if necessary<sup>1</sup>

In patients with existing diabetes, oral antidiabetic drugs may need to be increased, or insulin therapy started<sup>1</sup>

Refer children and adolescents to a paediatrician if growth suppression is suspected.<sup>1</sup>

If adrenal suppression is suspected, biochemical testing of the HPA axis should be considered after steroid treatment has been reduced to a physiological dose.<sup>2</sup>

Consider referral if fracture risk is high and/or BMD is decreasing<sup>2</sup>

If patient is considered to be at increased risk of a fragility fracture initiate treatment with an oral bisphosphonate<sup>1,3</sup>

### **Additional notes**

#### **Ensure that patient has been issued with a blue corticosteroid treatment card and that the treatment information is up to date**

Document person's history of chickenpox. Advise all those without a history of chickenpox who are taking systemic corticosteroids to avoid close contact with people who have chickenpox or shingles, and to seek urgent medical advice if they are exposed.

Symptoms of and/or exposure to serious infections should also be assessed as corticosteroids are contraindicated in patients with untreated systemic infections<sup>2</sup>

### **References**

1. NICE. Corticosteroids-oral: Monitoring. CKS (last revised Aug 2015) accessed via: <https://cks.nice.org.uk/corticosteroids-oral#!scenariorecommendation:5>
2. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy, Asthma & Clinical Immunology* 2013, 9:30. accessed via <http://www.aacijournal.com/content/pdf/1710-1492-9-30.pdf>
3. SIGN 142 Management of osteoporosis and the prevention of fragility fractures. Published Mar 2015. Available: <http://sign.ac.uk/pdf/SIGN142.pdf>
4. BNF. December 2016 – accessed via Medicines Complete

## Dabigatran

### Tests prior to starting treatment

Clotting screen, renal function/ creatinine clearance, LFTs, FBC<sup>2</sup>  
BP<sup>6</sup>

### Monitoring until patient is stabilised

Ideally assess patient every 3 months to:

- Assess compliance and reinforce advice regarding regular dosing schedule.
- Enquire about adverse effects such as bleeding.
- Assess for the presence of thromboembolic events
- Enquire about other medicines, including OTC medicines<sup>2</sup>

### Ongoing monitoring

- renal function, LFTs, FBC<sup>1,2,4,5</sup>
- Repeat U&E's every 6 months if CrCl 30–60 mL/min, patient > 75 years or fragile.<sup>2,4</sup>
- More frequent renal function/LFTs advised if intercurrent illness that may impact renal or hepatic function.<sup>2,5</sup>

### Action required if abnormal results

If renal function has declined, review treatment, as dabigatran may need to be stopped (if creatinine clearance is < 30ml/min) or a lower dose may be required.<sup>2,5</sup>

If there is an unexplained fall in haemoglobin and/or haematocrit, occult bleeding may be present.<sup>2</sup>

If the patient's HASBLED score is more than 3, then the patient is at a high risk of bleeding and dabigatran should be used cautiously, with regular reviews.<sup>6</sup>

LFTs are > 2x the upper limit of normal - the SPC for dabigatran states that there is no evidence to support use- therefore suggest that review treatment with specialist input if needed.

### Additional notes

The MHRA has advised that because of the significant risk of major bleeding, special care should be taken in patients with co morbidities, procedures and concomitant treatments and attention should be paid to renal function.<sup>3</sup>

**Commented [ED15]:** Renal function should be based on Cockcroft Gault calculation – a local protocol on guidance in extremes of body weight is advisable. SE London Guidance is available: <http://www.lambethccg.nhs.uk/news-and-publications/meeting-papers/south-east-london-area-prescribing-committee/Documents/Cardiovascular%20Disease%20Guidelines/Creatinine%20clearance%20guidance%20July%202017.pdf>

**Commented [d16]:** Needed in conjunction with renal function and liver function if want to calculate HAS-BLED score

**Commented [ED17]:** See comment above about assessment of renal function

## References

1. BNF accessed via Medicines Complete Dec 2016
2. CKS: Anticoagulation – oral. Scenario Dabigatran. Last updated Oct 2015.  
Available: <https://cks.nice.org.uk/anticoagulation-oral#!scenariorecommendation:12>
3. MHRA guidance. Drug Safety Update 2013; (revised Nov 2015)
4. HAS-BLED score for bleeding risk on oral anticoagulation in atrial fibrillation (AF). Accessed via: <http://www.mdcalc.com/has-bleed-score-major-bleeding-risk/>
5. SPC for dabigatran – last updated Jan 2016
6. UKCPA Handbook of per-operative medicines. Published Oct 2016.

## Digoxin

### Tests prior to starting treatment

Renal function<sup>1,7</sup>

U&Es<sup>1,2,3,7</sup> (paying particular attention to potassium and calcium levels) and magnesium levels [if on a long-term PPI or other drugs that may cause hypomagnesaemia<sup>8</sup>]

### Monitoring until patient is stabilised

Routine digoxin measurement is not recommended in clinically and biochemically stable patients, but may be warranted if there are changes in clinical state, concomitant use of drugs that may impact on toxicity, recognition of situations predisposing to toxicity, notably renal insufficiency.<sup>1,7</sup>

Samples for digoxin measurement should be taken at least 6 hours after the last dose<sup>5</sup>

### Ongoing monitoring

Routine monitoring of serum digoxin concentrations is not recommended.<sup>1,4,7</sup>

The presence of toxic symptoms such as nausea, vomiting, visual disturbance (yellow-green discoloration), or severe dysrhythmias may prompt an urgent measurement.<sup>1</sup>

A digoxin level may be useful to confirm a clinical impression of toxicity or non-adherence.<sup>4</sup>

Appropriate electrolyte monitoring should be carried out in patients predisposed to hypokalaemia (e.g. on loop diuretics), and in patients with renal dysfunction and in elderly people.<sup>3</sup>

CKS recommend U&Es and creatinine are monitored at least annually and more frequently in elderly patients or patients with renal impairment<sup>7</sup>

Magnesium levels should be checked periodically in patients taking long-term PPIs or other medicines that pre-dispose to hypomagnesaemia<sup>8</sup>

**Commented [d18]:** Local decision needed on approach to monitoring U&Es for at-risk patients.

### Action required if abnormal results

If toxicity occurs, digoxin should be withdrawn; serious manifestations require urgent specialist management. Digoxin-specific antibody fragments are available for reversal of life-threatening overdosage.<sup>5</sup>

Hypokalaemia, hypomagnesaemia and hypocalcaemia predispose the patient to digoxin related problems.<sup>5,7</sup>

If toxicity is suspected potassium level should also always be measured – if it is low, digoxin toxicity should be assumed without waiting for digoxin level.<sup>6</sup>

Low potassium levels require correction.<sup>5</sup>

## References

1. Smellie, WSA, Coleman JJ. Pitfalls of testing and summary of guidance on safety monitoring with amiodarone and digoxin. *BMJ* 2007;334:312-5
2. Aspen. Lanoxin 125 Tablets. SPC (date of revision Aug 2014)
3. Smellie WSA, Forth J, Sundar S. Best practice in primary care pathology: review 4. *J Clin Pathol.* 2006 September; 59 (9): 893–902
4. NICE. Chronic heart failure: Clinical guideline 108 (25 August 2010)
5. BNF – accessed via Medicines Complete December 2016
6. Aronson JK, Hardman M. ABC of monitoring drug therapy. Digoxin. *BMJ* 1992, 305: 1149-52
7. CKS. Atrial fibrillation, digoxin guideline (last revised Oct 2015). Available: <https://cks.nice.org.uk/atrial-fibrillation#!prescribinginfosub:10>
8. MHRA. Drug Safety Update - Proton pump inhibitors in long-term use: reports of hypomagnesaemia (April 2012). Available: <https://www.gov.uk/drug-safety-update/proton-pump-inhibitors-in-long-term-use-reports-of-hypomagnesaemia>

## Dronedarone

### Tests prior to starting treatment

LFTs<sup>1,3</sup>  
Serum creatinine<sup>1,3</sup>  
ECG<sup>1,3</sup>  
U&Es (potassium and magnesium)<sup>2</sup>

### Monitoring until patient is stabilised

LFTs after 7 days<sup>1,3</sup>  
Serum creatinine after 7 days<sup>1,3</sup>

### Ongoing monitoring

LFTs every month for 6 months then at months 9 and 12 and periodically thereafter.<sup>1</sup> South London Cardiac and Stroke Network recommend annual monitoring after 12 months.<sup>2</sup>

Renal function should be monitored periodically.<sup>1</sup> South London Cardiac and Stroke network recommend that serum creatinine is measured annually.<sup>2</sup>

ECG should be repeated every 6 months<sup>1</sup>

### Action required if abnormal results

Discontinue treatment if 2 consecutive alanine aminotransferase concentrations exceed 3 times upper limit of normal.<sup>3</sup> There should be a gap of between 48 to 72 hours between measurements.<sup>4</sup>

Dronedarone should not be initiated in patients if eGFR is less than 30 mL/minute/1.73 m<sup>2</sup>.<sup>3</sup>

Dronedarone is contraindicated in patients with severe hepatic impairment

A slight increase in serum creatinine (average 10 µmol/l) is expected within 7 days of starting dronedarone. If an increase is observed creatinine should be measured after another 7 days.<sup>4</sup> Further increases should prompt consideration of treatment discontinuation.<sup>1</sup> However South London Cardiac and Stroke Network advise that treatment should only be discontinued if eGFR drops to less than 30 mL/minute/1.73 m<sup>2</sup>.

If AF recurs during treatment consider cessation of dronedarone and if permanent AF develops the drug should be discontinued.<sup>1</sup>

Within the SPC it is advised that if QTc Bazett interval is  $\geq 500$  milliseconds, dronedarone should be stopped.<sup>4</sup>

South London Cardiac and Stroke Network advise that treatment should not be initiated until hypokalaemia and hypomagnesaemia have been rectified.<sup>2</sup>

**Commented [d19]:** Needs local agreement on whether annual monitoring of LFTs and renal function is reasonable after 12 months

Patients or their carers should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as abdominal pain, anorexia, nausea, vomiting, fever, malaise, itching, dark urine, or jaundice develop.<sup>3</sup> Patients or their carers should be told how to recognise signs of heart failure and advised to seek prompt medical attention if symptoms such as weight gain, dependent oedema, or dyspnoea develop or worsen.<sup>3</sup> Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity and patients should be carefully evaluated clinically.<sup>4</sup>

### References

1. MHRA Drug Safety Update Oct 2011, vol 5 issue 3: A1. Accessed via <https://www.gov.uk/drug-safety-update/dronedarone-multaq-cardiovascular-hepatic-and-pulmonary-adverse-events-new-restrictions-and-monitoring-requirements> (last revised Dec 2014)
2. Dronedarone for the maintenance of sinus rhythm in patients with non-permanent (paroxysmal/ persistent) atrial fibrillation (AF). South London Cardiac and Stroke Network. Published Nov 2011. Accessed via <http://www.slcsn.nhs.uk/files/prescribing/dronedarone-102011.pdf> (still available but past review date)
3. BNF accessed via Medicines Complete December 2016
4. Sanofi-Aventis. Summary of Product Characteristics for Multaq (Dronedarone). Last updated Sep 2014. Accessed via <http://www.medicines.org.uk/emc/medicine/22894/SPC/>

## Edoxaban

### Tests prior to starting treatment

Body weight<sup>1,2</sup>

Renal function (CrCl)<sup>1-3,5</sup>

U&Es<sup>3</sup>

Baseline Clotting Screen<sup>3</sup>

Full blood count<sup>3</sup>

LFTs<sup>2,3</sup>

BP<sup>2,3</sup>

**Commented [ED20]:** Renal function should be based on Cockcroft Gault calculation – a local protocol on guidance in extremes of body weight is advisable. SE London Guidance is available: <http://www.lambethccg.nhs.uk/news-and-publications/meeting-papers/south-east-london-area-prescribing-committee/Documents/Cardiovascular%20Disease%20Guidelines/Creatinine%20clearance%20guidance%20July%202017.pdf>

### Monitoring until patient is stabilised

No routine anticoagulant monitoring is needed<sup>1,2,4,5</sup>.

First follow-up appointment should be after 1 month<sup>5</sup>, then ideally assess every 3 months<sup>3,4</sup> (or more frequently if required) to<sup>3-5</sup>:

- Assess compliance
- Enquire about adverse effects such as bleeding
- Assess for the presence of thromboembolic events
- Enquire about other medicines, including OTC medicines

**Commented [ED21]:** Needed in conjunction with renal function and liver function if want to calculate HAS-BLED score

### Ongoing monitoring

Clinical monitoring of compliance, adverse effects e.g. signs of bleeding, thromboembolism and concurrent medicines as detailed above.

U&Es, Cr, LFTs, FBC at least once a year<sup>3-5</sup>.

U&Es, Cr, LFTs, FBC 6-monthly if the patient is older than 75 years or fragile<sup>4,5</sup>.

Repeat U&Es and Cr every 6 months if CrCl 30-60mL/min; or every 3 months if CrCl 15-30mL/min<sup>3,4</sup>. The EHRA guidance suggests retesting every  $x$ -months (where  $x = \text{CrCl}/10$ ) [e.g. if CrCl 30mL/min every 3 months, if CrCl 20mL/min every 2 months]<sup>5</sup>.

More frequent blood monitoring is advised when a change in renal function is suspected or where intercurrent illness, or concomitant medicinal products may impact on renal or hepatic function<sup>1-5</sup>.

**Commented [ED22]:** See comment above about assessment of renal function

### Action required if abnormal results

In patients with CrCl < 15mL/min or undergoing dialysis edoxaban should be avoided<sup>1,2</sup>. Assess for bleeding and seek advice regarding alternative anticoagulant therapy.

Manufacturer advises reduce dose to 30mg once daily in moderate to severe renal impairment (CrCl 15-50mL/min)<sup>1,2</sup>.

Manufacturer advises avoid in severe hepatic impairment<sup>1</sup>, or hepatic disease associated with coagulopathy and clinical relevant bleeding<sup>2</sup>.

If liver enzymes are elevated (ALT/AST > 2 x ULN) or total bilirubin  $\geq 1.5$  x ULN, edoxaban should be used with caution (these patients were excluded from clinical trials)<sup>1,2</sup>.

A low haemoglobin may suggest that occult bleeding is occurring and may require further investigations<sup>2</sup>.

Stop if severe bleeding occurs<sup>1</sup>.

Reduce dose in low body weight  $\leq 60\text{kg}$ <sup>1,2</sup>.

### Additional notes

The Cockcroft-Gault method for calculating CrCl is recommended when assessing patients' renal function<sup>2,5</sup>.

A trend towards decreasing efficacy with increasing CrCl was observed compared to well-managed warfarin<sup>2</sup>. EMA advised that 'edoxaban should only be used in patients with high creatinine clearance after a careful evaluation of the individual thrombo-embolic and bleeding risk<sup>5</sup>. In the US, edoxaban is not licensed in patients with CrCl > 95 mL/min, due to reduced efficacy<sup>6</sup>.

If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, edoxaban should be stopped as soon as possible and preferably at least 24 hours before the procedure<sup>2</sup>.

If the patient's HAS-BLED score is 3 or more anticoagulation should be used with caution and more regular reviews<sup>7</sup>.

### References

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## Eplerenone

### Tests prior to starting treatment

U&Es (including creatinine) and eGFR<sup>1,3,4</sup>

### Monitoring until patient is stabilised

U&Es (including Creatinine) and eGFR at 1, 4, 8 and 12 weeks, and 1 and 4 weeks after any dose increase.<sup>1,2,3,4</sup>

In the treatment of early post myocardial infarction patients with heart failure the monitoring of U&Es (including Creatinine) and eGFR is advised after 48 hours as well as at the above time intervals<sup>3</sup>.

### Ongoing monitoring

U&Es (including Creatinine) and eGFR at 6 months and every 3 to 6 months thereafter.<sup>2,3,4</sup>

**Commented [d23]:** Needs local agreement on frequency of monitoring

### Action required if abnormal results

The manufacturers state eplerenone should not be started in patients with a baseline serum potassium >5.0mmol/L, an eGFR < 30mL/minute per 1.73 m<sup>2</sup> or severely impaired liver function (Childs-Pugh Class C).<sup>1</sup> However, NICE state to consider seeking specialist advice if concerned about an increased risk of developing serious hyperkalaemia, for example in those with reduced renal function and or if baseline serum potassium is greater than 5 mmol/L<sup>3</sup>.

NICE state the decision whether to stop or reduce aldosterone antagonists in light of rises of serum creatinine and potassium or a decline in eGFR, should be made by a specialist<sup>4</sup>.

NICE support the following recommendations:

Halve the dose of eplerenone if the potassium rises to >5.5-5.9 mmol/L.

Stop if potassium rises to >6.0mmol/L or serum creatinine rises to >220micromol/L and seek specialist advice<sup>3,4</sup>.

### Additional notes

Advise patients to avoid NSAIDs not prescribed by a physician (self purchases 'over the counter') and salt substitutes high in potassium<sup>2,3</sup>.

## References

1. Summary of Product Characteristics for Inspira® 25mg film-coated tablets (eplerenone). Date of revision of the text March 2016 Accessed via [www.medicines.org.uk/emc/medicine/16746](http://www.medicines.org.uk/emc/medicine/16746) on 25/10/2016
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## Hydroxycarbamide

### Tests prior to starting treatment

FBC, U&Es (incl renal function), uric acid, LFTs, <sup>1,2,3,6</sup>.  
Reticulocyte count, HbF% and lactate dehydrogenase (LDH) recommended when used in Sickle Cell disease<sup>5</sup>

Consider NICE recommendations regarding screening for hepatitis B and C in patients at increased risk of infection <sup>4</sup>

### Monitoring until patient is stabilised

#### In Sickle Cell

Weekly FBC for first four weeks then every two weeks for next 8 weeks if stable<sup>5</sup>.  
BNF recommends monitoring FBC every 2 weeks for first 2 months<sup>7</sup>.

#### In psoriasis

Weekly FBC until an effective dose is established<sup>2</sup>

### Ongoing Monitoring

#### In sickle cell

Monthly FBC if blood counts stable and 3 monthly U+Es, LFTs, Urate, LDH and HbF%<sup>5</sup>. However BNF recommends FBC every 2 months unless on maximum dose in which case FBC should continue to be monitored every 2 weeks<sup>6</sup>

#### In psoriasis

FBC every 1-3 months<sup>2</sup>

Serum creatinine, uric acid and LFTs should also be monitored<sup>1</sup>

**Commented [d24]:** Frequency needs to be agreed locally

### Action required if abnormal results

If neutrophils  $< 1.5 \times 10^9/L$ , platelets  $< 80 \times 10^9/L$ , reticulocytes  $< 10 \times 10^9/L$  or Hb drops by  $>3g/dL$  from baseline stop hydroxycarbamide until blood counts have recovered<sup>5</sup>

If creatinine clearance  $< 60ml/min$  review initiate treatment at half dose<sup>5</sup>

### Additional notes

Patients receiving long-term therapy with hydroxycarbamide should be advised to protect skin from sun exposure<sup>6</sup>

Patients should be advised to avoid live vaccinations<sup>6</sup>

Patients receiving long-term therapy for malignant disease should be monitored for secondary malignancies<sup>6</sup>.

## References

1. Summary of Product Characteristics for Hydrea Caps 500mg (hydroxycarbamide). Date of revision of the text June 2015.
2. British Association Dermatologists – Patient information leaflet for hydroxycarbamide (formerly hydroxyurea). Available: <http://www.bad.org.uk/shared/get-file.ashx?id=91&itemtype=document>
3. Summary of Product Characteristics for Siklos 1000mg tablets (hydroxycarbamide). Date of revision of the text Mar 2014
4. NICE public health guidance 43: Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (2012)
5. Scottish Paediatric and Adult Haemoglobinopathy Managed Clinical Network – Management Guidelines for adults with sickle cell disease (2012).
6. BNF – accessed via Medicines Complete Dec 2016.

## **Hydroxychloroquine**

### **Tests prior to starting treatment**

Height <sup>1,2</sup>  
Weight <sup>1,2 \*</sup>  
BP <sup>1,2</sup>  
FBC <sup>1,2,5</sup>  
Calculated GFR <sup>1,2,3,5</sup>  
ALT and/or AST <sup>1,2,3,5</sup>  
Albumin <sup>1,2</sup>

### **Initial ophthalmological examination**

BSR/BHPR 2017 guidelines state that patients should have baseline formal ophthalmic examination, ideally including objective retinal assessment for example using optical coherence tomography, within 1 year of commencing an antimalarial drug. <sup>1,2</sup>

All individuals taking hydroxychloroquine who have additional risk factors for retinal toxicity may be screening annually from the baseline visit or annual screening commenced before 5 years of treatment completed. This is to be decided by a Consultant ophthalmologist following the baseline visit <sup>4</sup>.

Additional risk factors: Concomitant tamoxifen use, impaired renal function (estimated glomerular filtration rate of less than 50ml/min/1.73m<sup>2</sup>), dose of hydroxychloroquine greater than 5mg/kg/day

### **Monitoring until patient is stabilised**

None identified <sup>1,2</sup>.

### **Ongoing monitoring**

No routine laboratory monitoring <sup>1,2</sup>.

Annual eye assessment (ideally including optical coherence tomography) if continued for > 5 years <sup>1,2</sup>.

### **Action required if abnormal results**

Adjust dose and/or increase screening frequency if impaired renal or liver function <sup>1,2,5</sup>

If visual impairment or eye disease is present prior to treatment, assessment by an optometrist is advised and any abnormality should be referred to an ophthalmologist. <sup>1,2</sup>

If visual acuity changes or patient develops blurred vision during treatment, refer to ophthalmologist, warn patient to stop treatment and seek initial prescriber's advice <sup>4</sup>.

\*Additional notes

To avoid excessive dosage the dose should not exceed 6.5mg/kg/day calculated from ideal body weight and not actual body weight <sup>5</sup>. Weight should be checked routinely to ensure the milligram/kg dose is still appropriate.

Concurrent tamoxifen use increases the risk of toxicity, patients need careful dosing and screening <sup>4</sup>

**References**

1. The BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Ledingham J et al. Accessed [here](#) 8/8/2017
2. The BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs – executive summary. Rheumatology 2017;56:865868
3. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press. Accessed online via: <https://bnf.nice.org.uk/> on 8/8/2017
4. Hydroxychloroquine and chloroquine retinopathy : recommendations for screening (draft July 2017) The Royal College of Ophthalmologists. Accessed [here](#) on 8/8/2017
5. Zentiva. Summary of Product Characteristics for Plaquenil-Hydroxychloroquine sulfate 200mg tablets. Last updated on the eMC 18/7/2017. Accessed online via: <http://www.medicines.org.uk/emc/> on 8/8/2017.

## Leflunomide

### Tests prior to starting treatment

BSR recommend that all patients starting DMARDs should have baseline measurement of height, weight and BP<sup>1</sup>

FBC (BNF specifies with differential white cell count and platelet count)<sup>1,2</sup>

Renal profile (creatinine/calculated GFR)<sup>1</sup>

Serum albumin<sup>1</sup>

ALT and/or AST<sup>1</sup> (BNF just recommends LFTs)<sup>2</sup>

There is a strong rationale for screening for hepatitis B and C in patients at increased risk of infection<sup>1</sup>.

Baseline HIV status should also be established in those with risk factors<sup>1</sup>.

Screening for lung disease should be undertaken at clinical discretion on a case-by-case basis.<sup>1</sup>

### Monitoring until patient is stabilised

FBC, creatinine/calculated GFR, ALT and/or AST, albumin every two weeks until dose stable for at least 6 weeks then monthly thereafter for 3 months. More frequent monitoring may be required in high-risk patients.<sup>1</sup>

Following a change in dose repeat FBC and LFTs, ALT and/or AST, creatinine/calculated GFR and albumin every 2 weeks until dose stable for 6 weeks and then revert to previous schedule.<sup>1</sup>

Alternatively BNF recommends FBC (incl differential WBC and platelets) and LFTs every two weeks for first 6 months.<sup>2</sup>

BSR recommend that weight and BP are measured at every monitoring visit.<sup>1</sup>

### Ongoing monitoring

Once the maintenance dose has been achieved and stable for 3 months consider monitoring

- FBC
- creatine/calculated GFR
- albumin
- ALT and/or AST

At least every 12 weeks. More frequent monitoring is appropriate in patients at higher risk of toxicity.<sup>1</sup>

Alternatively BNF recommends FBC (incl differential WBC and platelets) and LFTs every 8 weeks.<sup>2</sup>

**Commented [ED25]:** Local decision needed on whether to follow BSR or BNF advice

BP and weight should be checked at each monitoring visit.<sup>1</sup>

#### **Action required if abnormal results**

Withhold treatment until discussion with consultant specialist if 1:

- WCC < 3.5 x 10<sup>9</sup>/L,
- Neutrophils < 1.6 x 10<sup>9</sup>/L
- Unexplained eosinophilia > 0.5x 10<sup>9</sup>/L
- Platelets < 140 x 10<sup>9</sup>/l,
- AST and/or ALT increase to >100units/ml
- Unexplained fall in serum albumin <30g/L
- MCV > 105f/L
- Creatinine increase > 30% above baseline over 12 months and/or calculated GFR < 60ml/min/1.73m<sup>2</sup>

CKS advise that the following symptoms may be a sign of leflunomide toxicity. Withhold until discussion with rheumatologist if <sup>3</sup>:

- Rash or itch ,
- Hair loss,
- Severe sore throat or abnormal bruising (check FBC immediately)
- Hypertension (BP>140/90) despite standard anti-hypertensives,
- Breathlessness,
- Unexplained weight loss >10% Severe or persistent headache or GI upset (nausea, diarrhoea)

#### **References**

1. BSR and BHPR non-biologic DMARD guidelines (2017). Available: [http://www.rheumatology.org.uk/includes/documents/cm\\_docs/2016/f/full\\_dmards\\_guideline\\_and\\_the\\_executive\\_summary.pdf](http://www.rheumatology.org.uk/includes/documents/cm_docs/2016/f/full_dmards_guideline_and_the_executive_summary.pdf)
2. BNF . Accessed via Medicines Complete. Last updated July 2017
3. NICE CKS. DMARDs: Scenario – leflunomide. Last updated July 2015

## **Lithium**

### **Tests prior to starting treatment**

Renal function and U&Es (DTB recommends particular attention to Na and creatinine: NICE recommend particular attention to calcium)<sup>1,3,4,7</sup>  
TFTs<sup>1,3,4,7</sup>

Cardiac function (ECG recommended for patients with risk factors for, or existing CVD)<sup>1,7</sup>

FBC<sup>7</sup>

Baseline measurement of weight (and height)/ BMI is desirable<sup>1,7</sup>

Lithium level if switching from another brand/ preparation<sup>3</sup>

Additionally, as part an annual review of physical health, NICE recommend that patients with bipolar disorder have baseline CV status assessment including pulse and BP, lipid profile, fasting blood glucose levels, liver function and HbA1c<sup>7</sup>

### **Monitoring until patient is stabilised**

#### **Plasma levels**

NICE and BNF recommend levels checked one week after starting and one week after every dose change. NICE advice is to maintain level between 0.6 and 0.8mmol/L (a level of between 0.8 and 1.0mmol/L may be appropriate in patients who have relapsed previously or who have sub-threshold symptoms with functional impairment<sup>7</sup>). Levels should be monitored weekly until stable. BNF state that a target serum-lithium concentration of 0.8–1 mmol/litre is recommended for acute episodes of mania, and for patients who have previously relapsed or have sub-syndromal symptoms but levels at the lower end of the range 0.4-1.0mmol/L may be acceptable in maintenance therapy and in elderly patients

SLAM also recommend measurement of plasma drug levels after 7 days, then 7 days after every dose change until the desired level is reached, 0.4mmol/L may be effective in unipolar depression, 0.6-1.0 mmol/L in bipolar illness, slightly higher levels in difficult-to-treat mania<sup>1</sup>

### **Ongoing Monitoring**

#### **Thyroid monitoring**

NICE and BNF recommend TFTs every 6 months<sup>2,7</sup> (more often if there is evidence of impaired thyroid function or an increase in mood symptoms that might be related to impaired thyroid function)

### **Plasma levels**

NICE and BNF recommend monitoring levels every 3 months. The BNF states that drug level monitoring should be continued every 3 months but NICE state that after 12 months monitoring can be decreased to every 6 months unless patients are elderly, taking drugs that interact with lithium, have impaired renal function, have impaired thyroid function, raised calcium levels, poor symptom control, poor adherence, or their most recent lithium level was  $\geq$  to 0.8mmol/L.

NICE also recommend that levels should be monitored more frequently if urea levels and creatinine levels become elevated, or eGFR falls over 2 or more tests

SLAM recommend levels should be monitored every 6 months unless patient is being prescribed interacting medicines, is elderly, has established renal impairment or other relevant physical illness when more frequent monitoring is advised<sup>1</sup>.

DTB recommends checking every 1-2 months for the first 6 months and then every 3-6 months if levels are stable and adherence is good<sup>4</sup>.

Priadel SPC states that the period between subsequent measurements can be increased gradually following stabilisation, but should not normally exceed 2-3 months<sup>3</sup>.

BNF recommends additional measurements be made if a patient develops significant intercurrent disease or if there is a significant change in their sodium or fluid intake<sup>2</sup>. Priadel SPC also recommends additional monitoring when there are signs of manic or depressive relapse, or lithium toxicity<sup>3</sup>.

### **Other monitoring**

NICE and DTB recommends annual calcium checks<sup>4,7</sup>.

Additionally NICE recommend that all patients with bipolar disorder should have annual physical health reviews at least annually which includes<sup>7</sup>

- weight or BMI, diet, nutritional status and level of physical activity
- cardiovascular status, including pulse and blood pressure
- metabolic status, including fasting blood glucose, glycosylated haemoglobin (HbA<sub>1c</sub>) and blood lipid profile
- liver function

### **Action required if abnormal results**

#### **Plasma levels**

NICE/BNF states serum lithium levels should be maintained between 0.6 and 1.0 mmol/l

Serum lithium level range depends on whether taken once or twice daily and whether level measured at 12 or 24 hours<sup>3</sup>

Toxic effects reliably occur at levels  $>1.5\text{mmol/L}$ <sup>1</sup>. If signs of toxicity are present, stop treatment, check plasma levels, and take steps to reverse the toxicity. A concentration of  $>2\text{mmol/L}$  requires urgent treatment<sup>2</sup>.

More frequent testing should be undertaken if there is evidence of clinical deterioration, abnormal results, a change in sodium intake, or symptoms suggesting abnormal renal or thyroid function (e.g. unexplained fatigue) or other risk factors (e.g. patient starting interacting medication)<sup>7</sup>

If urea and creatinine levels become elevated, initiate closer monitoring of dose and blood levels and assess the rate of renal function deterioration<sup>7</sup>.

The NPSA alert supporting information states that the management of subclinical hypothyroidism remains controversial, but the following approach has been suggested. If the serum TSH is confirmed to be above twice the 'normal' limit, for example a laboratory may report this situation with TSH test results above  $10\text{mU/L}$ , then there is a high risk of progression to overt hypothyroidism and levothyroxine should be prescribed. If the value is between 5 and  $10\text{mU/L}$  more frequent monitoring is indicated and a trial of levothyroxine may be appropriate particularly if the patient is symptomatic.<sup>9</sup>

#### **Additional notes**

**Stopping lithium:** NICE recommend that when stopping lithium the dose should be reduced gradually over at least 4 weeks, and preferably up to 3 months, even if the person has started taking another antimanic drug. During dose reduction and for 3 months after lithium treatment is stopped, monitor the person closely for early signs of mania and depression<sup>7</sup>. SLAM recommend that incremental reductions in plasma levels of  $>0.2\text{mmol/L}$  should be avoided<sup>1</sup>

A lithium treatment pack should be given to all patients on initiation of therapy and they should receive appropriate ongoing verbal and written information. The record book should be used to track blood levels.<sup>2,9</sup> Prescribers and pharmacists should check blood levels are monitored regularly and that it is safe to issue a repeat prescription and/or dispense the prescribed item<sup>9</sup>. Systems to identify and deal with medicines that might adversely interact with lithium therapy should be in place<sup>9</sup>.

Ideally blood samples for plasma lithium level estimations should be taken 12 hours post-dose in patients prescribed a single daily dose of a prolonged-release preparation<sup>1</sup>. In practice an interval of 10-14 hours is acceptable as long as the interval is the same at each measurement and the delay after the dose noted<sup>4</sup> NICE recommend that patients should be advised that erratic compliance or rapid discontinuation may increase the risk of manic relapse. Monitor older adults carefully for symptoms of lithium toxicity because they may develop high serum levels of lithium at doses in the normal range, and lithium toxicity is possible at moderate serum levels.<sup>7</sup>

Patients should be advised to:

- avoid dietary changes which reduce or increase sodium intake<sup>2</sup>
- seek medical attention if they develop diarrhoea and/or vomiting<sup>7</sup>

- report the signs and symptoms of lithium toxicity, hypothyroidism, renal dysfunction and benign intracranial hypertension.<sup>2</sup>
- ensure they maintain their fluid intake, particularly after sweating (for example, after exercise, in hot climates or if they have a fever), if they are immobile for long periods or if they develop a chest infection or pneumonia<sup>7</sup>
- Patients taking lithium should be warned not to take OTC NSAIDs<sup>7</sup>

NICE recommend that patients are monitored for signs of neurotoxicity (including paraesthesia, ataxia, tremor and cognitive impairment) which can occur at therapeutic levels<sup>7</sup>

SLAM state that there is no clinically significant difference in the pharmacokinetics of Priadel and Camcolit. Other preparations should not be assumed to be bioequivalent and should be prescribed by brand.<sup>1</sup>

SLAM also note that lithium citrate liquid is available in two strengths (equivalent to 200mg and 400mg lithium carbonate in 5ml) and that care is needed when prescribing and dispensing to ensure that patient receives the intended dose.

The following measures are QOF indicators for 2016/17<sup>5</sup>:

- percentage of patients on lithium with a record of serum TSH in the preceding 9 months
- percentage of patients on lithium with a record of serum creatinine in the preceding 9 months
- percentage of patients with a record of lithium levels in the therapeutic range in the preceding 4 months
- The percentage of patients with schizophrenia, bipolar affective disorder and other psychoses who have a record of blood pressure in the preceding 12 months

## References

1. The South London and Maudsley NHS Foundation Trust and Oxleas NHS Foundation Trust Prescribing Guidelines in Psychiatry (12th edition)
2. BNF: accessed via Medicines Complete Dec 2016
3. Summary of Product Characteristics for Priadel 400mg prolonged-release tablets, Date of revision of text Jun 2015
4. Using lithium safely DTB 1999, 37, 3
5. 2016/17 general medical services (GMS) contract quality and outcomes framework (QOF)  
<http://www.nhsemployers.org/~media/Employers/Documents/Primary%20care%20contracts/QOF/2016-17/2016-17%20QOF%20guidance%20documents.pdf>
6. UK Guidelines for thyroid function tests by Assoc. Clinical Biochemistry, British Thyroid Assoc and British Thyroid Foundation (Jul 2006)
7. NICE Guideline on the management of bipolar disorder in adults, children and adolescents in primary and secondary care (last updated Feb 2016)
8. Best practice in primary care pathology: review 5. J Clin Pathol 2006; 59: 1229-37
9. National Patient Safety Agency National Reporting and Learning Service: Patient Safety Alert (NPSA/2009/PSA005) Safer Lithium Therapy (December 2009)

## Mercaptopurine

### Tests prior to starting treatment

FBC<sup>1,8</sup>

LFTs<sup>1,2</sup>

U&Es including creatinine<sup>1,2</sup>

TPMT assay<sup>1,2,7</sup>

Consider NICE recommendations regarding screening for hepatitis B and C in patients at increased risk of infection<sup>6</sup>

Baseline HIV status should be established in those with risk factors<sup>4</sup>

### Monitoring until patient is stabilised

BNF recommends monitoring LFTs (frequency unspecified)

CKS recommends FBC every 2-4 weeks for 2 months and LFTs every week for 6 weeks then every 2 weeks until dose is stable for 6 weeks.<sup>1</sup>

BSG state that monitoring FBC every 2 to 4 weeks for 2 months and then every 4 to 8 weeks is considered fairly common practice<sup>3</sup>.

GI specialists from Guys & St Thomas NHS Foundation Trust suggest monitoring FBC and LFTs at weeks 2, 4, 8 and 12.<sup>7</sup>

They also recommend that the methylmercaptopurine to thioguanine ratio (MeMP:TGN) is measured at Week 4 and 16 (and at Week 4 after each dose change).

### Ongoing monitoring

BNF recommends monitoring LFTs (frequency unspecified)

CKS recommend monitoring FBC every 4 to 8 weeks, LFTs every month but once stable for 6 months consider reducing to 3-monthly and U&Es (incl creatinine) every 6 months.<sup>1</sup>

BSG suggest monitoring FBC every 4 to 8 weeks<sup>3</sup>

GI specialists from Guys & St Thomas NHS Foundation Trust suggest monitoring FBC and LFTs every 3 months and that the methylmercaptopurine to thioguanine ratio (MeMP:TGN) is measured annually<sup>7</sup>.

### Action required if abnormal results

CKS advise that treatment with mercaptopurine should be withheld until discussion with consultant specialist if:<sup>1</sup>

- WBC < 3.5 x 10<sup>9</sup>/l,
- Neutrophils < 2 x 10<sup>9</sup>/l

**Commented [d26]:** NICE states that TPMT activity should be assessed before offering patients with Crohn's disease treatment with azathioprine or mercaptopurine, and that treatment should not be offered to those with deficient (very low or absent) activity. Consider offering a lower dose to those with below normal (but not deficient) activity<sup>5</sup>

**Commented [ED27]:** It is unclear if this test is routinely available or used.

- Platelets < 150 x 10<sup>9</sup>/l,
- AST, ALT increase to > twice the upper limit of normal

If patient develops renal impairment (eGFR < 50ml/min) check dosing with specialist

If MCV > 105fl: check B12, serum folate and TSH – withhold until results are available and discuss with specialist<sup>1</sup>

### **Additional notes**

Pneumococcal vaccine and annual flu vaccine should be given, but live vaccines should be avoided<sup>5</sup>.

In patients exposed to chickenpox or shingles, passive immunisation should be carried out using VZIG.

Patients should be warned to report immediately any signs or symptoms of bone marrow suppression (e.g. inexplicable bruising or bleeding)<sup>2</sup> or liver impairment (e.g. new onset jaundice)<sup>4</sup>

Sunscreens and protective clothing should be encouraged to reduce sunlight exposure<sup>1</sup>

### **References**

1. CKS. Crohn's Disease – azathioprine and mercaptopurine. Last revised April 2015
2. BNF – accessed via Medicines Complete (updated August 2017)
3. BSG Guidelines for the management of inflammatory bowel disease in adults (2011) – Gut 2011; 60:571-607
4. British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011
5. NICE Crohn's disease: management in adults, children and young people (CG152) (last updated May 2016)
6. NICE public health guidance 43 (2012): Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (last updated Mar 2013)
7. A practical guide to thiopurine prescribing and monitoring in IBD. Frontline Gastroenterology 2016;0:1–6. doi:10.1136/flgastro-2016-100738. Available: <http://fg.bmj.com/content/flgastro/early/2016/08/29/flgastro-2016-100738.full.pdf>

## **Mesalazine**

### **Tests prior to starting treatment**

Renal function should be assessed prior to starting treatment. <sup>1,2</sup>

U&Es.<sup>3</sup>

LFTs<sup>3</sup>

### **Monitoring until patient is stabilised**

U&Es should be monitored every 3 months for the first year.<sup>3</sup>

Renal function should be monitored every 3 months for the first year.<sup>2</sup>

LFTs should be monitored every 3 months for the first year.<sup>3</sup>

### **Ongoing monitoring**

U&Es should be monitored every 6 months or annually based on the person's risk factors.<sup>3</sup>

Renal function should be monitored annually or more frequently in renal impairment.<sup>1-4</sup>

LFTs should be monitored every 6 months or annually based on the person's risk factors.<sup>3</sup>

### **Action required if abnormal results**

Mesalazine should be discontinued if renal function deteriorates.<sup>2-4</sup>

AST, ALT > twice upper limit of reference range, withhold treatment until discussed with the specialist team.<sup>3</sup>

### **Additional notes**

Haematological investigations should be performed if the patient develops unexplained bleeding, bruising, purpura, anaemia, fever or sore throat. Treatment should be stopped if there is suspicion or evidence of blood dyscrasia.<sup>2</sup>

### **References**

1. British National Formulary. Accessed online via: <http://www.medicinescomplete.com> on 14/07/2016.
2. Summary of Product Characteristics for Asacol® 400mg MR Tablets (mesalazine). Last updated on the eMC 14/07/2016. Accessed online via: <http://www.medicines.org.uk/emc/> on 14/07/2016.
3. CKS July 2015. Ulcerative colitis. Accessed online via: <http://cks.nice.org.uk/> on 14/07/2016.
4. BSG Guidelines for the management of inflammatory bowel disease in adults (2011) – Gut 2011, 60(5): 571-607.

## **Methotrexate**

### **Tests prior to starting treatment**

BSR recommend that all patients starting DMARDs should have baseline measurement of height, weight and BP<sup>1</sup>

FBC

Renal profile (creatinine/calculated GFR)<sup>1,4</sup>

Serum albumin<sup>1</sup>

ALT and/or AST<sup>1</sup> (BNF states LFTs)

BSG suggest FBC and LFTs when used to treat IBD<sup>8</sup>

Consider NICE recommendations regarding screening for hepatitis B and C in patients at increased risk of infection<sup>1,11</sup>

Baseline HIV status should also be established in those with risk factors <sup>1</sup>.

Screening for lung disease should be undertaken at clinical discretion on a case-by-case basis.<sup>1</sup>

### **Monitoring until patient is stabilised**

#### **IN GENERAL**

BNF recommends FBC, renal and liver function every 1-2 weeks until therapy is stabilised.<sup>4</sup>

#### **RHEUMATOLOGY**

FBC, creatinine/calculated GFR, ALT and/or AST, albumin every two weeks until dose stable for at least 6 weeks then monthly thereafter for 3 months. More frequent monitoring may be required in high-risk patients.<sup>1</sup>

Following a change in dose repeat FBC ALT and/or AST, creatinine/calculated GFR and albumin every 2 weeks until dose stable for 6 weeks and then revert to previous schedule<sup>1</sup>

#### **DERMATOLOGY**

Previously BSR/BAD recommended FBC, U&Es, creatinine and LFTs weekly and gradually increase interval until therapy stabilised. However it is not yet clear if BAD will endorse revised BSR Guidance outlined above

#### **GASTROENTEROLOGY**

BSG suggest that FBC and LFTs should be checked once within 4 weeks of starting treatment when used to treat IBD and then every month<sup>8</sup>

**Commented [ED28]:** Local decision needed as to whether to encourage all specialties to use revised BSR Guidance or use BNF recommendations.

## Ongoing monitoring

### IN GENERAL

CSM and BNF recommend FBC, U&Es, renal function and LFTs every 2-3 months once stabilised<sup>3,4,5</sup>

**Commented [d29]:** A local policy outlining whether endorsing these general monitoring recommendations is more realistic than supporting differing recommendations for each indication is needed

CKS advise that provided patients are stable for 6 weeks after the last dose increase; FBC, LFTs and renal function can be monitored monthly. Once the disease and dose have been stable for 12 months, monitoring can be reduced to every 2-3 months following discussion with the specialist.

### RHEUMATOLOGY

Once the maintenance dose has been achieved and stable for 3 months consider monitoring FBC, creatinine/calculated GFR, albumin, ALT and/or AST at least every 12 weeks.<sup>1</sup> More frequent monitoring is appropriate in patients at higher risk of toxicity.

Additionally the NPSA suggest that CRP, ESR or PV may be monitored every 3 months and creatinine every 3-6 months<sup>7</sup>.

### DERMATOLOGY

Previously BAD supported FBC, U&Es, creatinine and LFTs every 2-3 months once patient is stabilised<sup>1</sup>

**Commented [ED30]:** As highlighted above – it is not yet clear if BAD will endorse the recently published revised guidance from BSR

Best Practice series recommends that when used in patients with psoriasis monitoring of PIIINP every 2-3 months is available<sup>6</sup>. BAD also state that monitoring of PIIINP is recommended for early detection of liver disease<sup>1</sup> NICE recommends that PIIINP levels be used alongside standard LFTs to monitor for abnormalities during treatment, taking into account pre-existing risk factors (e.g. obesity, diabetes and alcohol use), baseline results and trends over time<sup>10</sup>

**Commented [d31]:** The practicalities of implementing this at a local level would need to be clarified – recommended for dermatology but not for rheumatology

### GASTROENTEROLOGY

BSG suggest that FBC and LFTs should be checked every month when used to treat IBD<sup>8</sup>

### Action required if abnormal results

BSR recommend that treatment be withheld until discussion with consultant specialist if:<sup>1</sup>

- WCC < 3.5 x 10<sup>9</sup>/L,
- Neutrophils < 1.6 x 10<sup>9</sup>/L
- Unexplained eosinophilia > 0.5 x 10<sup>9</sup>/L
- Platelets < 140 x 10<sup>9</sup>/l,
- AST and/or ALT increase to >100units/ml
- Unexplained fall in serum albumin <30g/L
- MCV > 105f/L
- Creatinine increase > 30% above baseline over 12 months and/or calculated GFR < 60ml/min/1.73m<sup>2</sup>

Annual flu vaccine should be given, but live vaccines should be avoided.<sup>1</sup>

Patients and their carers should be warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort and dark urine), and respiratory effects (e.g. shortness of breath).<sup>3,12</sup>

Patients should be advised to avoid self-medication with over-the-counter aspirin or ibuprofen.<sup>3</sup>

Patients should be counselled on the dose, treatment booklet, and the use of NSAIDs<sup>3</sup>

The NPSA advise that patients should be instructed to only take their methotrexate once a week on the same day each week and should be issued with a patient-held record card<sup>3,9</sup>

## References

1. BSR and BHPR non-biologic DMARD guidelines (2017).
2. Current problems in pharmacovigilance. Sept 2003 Vol 29 p 5
3. BNF – accessed via MedicinesComplete (Last updated July 2017)
4. Current Problems in Pharmacovigilance Sept 1997, Vol 23, 12
5. CKS Clinical Topic: DMARDs- methotrexate (last revised July 2015)
6. Best Practice in primary care pathology: review 10. J. Clin. Pathol 2007; 60: 1195-1204
7. NPSA. Methotrexate- patient held blood monitoring and dosage record book
8. BSG Guidelines for the management of inflammatory bowel disease in adults (2011) – Gut 2011, 60(5):571-607
9. NPSA: Improving compliance with oral methotrexate guidelines
10. NICE (2012) Psoriasis: The assessment and management of psoriasis (CG153)
11. NICE public health guidance 43 (2012): Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection
12. NHS England. Never Events List 2015/16. Published Mar 2015.

## **Minocycline**

### **Tests prior to starting treatment**

LFTs<sup>1</sup>  
Creatinine/ calculated GFR<sup>4</sup>

### **Monitoring until patient is stabilised**

None identified

### **Ongoing monitoring**

If treatment continued for longer than 6 months: Monitor every 3 months for hepatotoxicity, pigmentation and for systemic lupus erythematosus (SLE)<sup>1</sup>. Periodic laboratory evaluations of organ system function, including haematopoietic, renal and hepatic should be conducted<sup>2</sup>. Watch for hypersensitivity syndrome consisting of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following:

- hepatitis, pneumonitis, nephritis, myocarditis, pericarditis, fever and lymphadenopathy; or for lupus-like or serum sickness-like syndromes.

BSR state that no routine laboratory monitoring is required<sup>4</sup>

### **Action required if abnormal results**

Discontinue if the patient develops hepatotoxicity, unusual pigmentation, SLE or lupus-like syndrome, photosensitivity, raised intracranial pressure, hypersensitivity syndrome, serum sickness-like syndrome or if pre-existing SLE gets worse<sup>1</sup>. Review dose if calculated GFR is indicative of Moderate (Stage III) renal impairment. Minocycline is contraindicated in severe and established renal failure (Stage IV and V)

### **Additional notes**

In a NICE advice document, which has not been updated, the ongoing use of minocycline (in acne) is questioned in view of safety concerns, lack of evidence of benefit over alternative treatments and relatively high acquisition cost.<sup>2</sup>

## References

1. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press. Accessed online via: [http://www.evidence.nhs.uk/formulary/bnf/current on 23/6/2016](http://www.evidence.nhs.uk/formulary/bnf/current%20on%2023/6/2016)
2. Meda Pharmaceuticals. Summary of Product Characteristics for Minocin MR 100mg Modified Release Capsules. Last updated on the eMC 12 March 2014 Accessed online via: <http://www.medicines.org.uk/emc/> on 23/6/2016
3. NICE advice [KTT11]. Minocycline (January 2015). Accessible via: <https://www.nice.org.uk/advice/ktt11>
4. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Published 2017.

## **Mycophenolate**

### **Tests prior to starting treatment**

BSR recommend that all patients starting DMARDs should have baseline measurement of height, weight and BP<sup>1</sup>

In females of child-bearing potential, exclude pregnancy immediately before treatment.<sup>2</sup> Mycophenolate mofetil or mycophenolic acid treatment should only be initiated in women of child bearing potential when there is a negative pregnancy test result to rule out unintended use in pregnancy<sup>4</sup>

FBC

Renal profile (creatinine/calculated GFR)<sup>1</sup>

Serum albumin<sup>1</sup>

ALT and/or AST<sup>1</sup>

There is a strong rationale for screening for hepatitis B and C in patients at increased risk of infection<sup>1,5,6</sup>

Baseline HIV status should also be established in those with risk factors<sup>1,4</sup>.

Screening for lung disease should be undertaken at clinical discretion on a case-by-case basis.<sup>1</sup>

### **Monitoring until patient is stabilised**

FBC, creatinine/calculated GFR, ALT and/or AST, albumin every two weeks until dose stable for at least 6 weeks then monthly thereafter for 3 months. More frequent monitoring may be required in high-risk patients.<sup>1</sup>

Following a change in dose repeat FBC ALT and/or AST, creatinine/calculated GFR and albumin every 2 weeks until dose stable for 6 weeks and then revert to previous schedule<sup>1</sup>

BNF recommends FBC every week for 4 weeks then twice a month for 2 months then every month in the first year<sup>2</sup>

In females of child-bearing potential, exclude pregnancy whilst on treatment.<sup>2,4</sup>

### **Ongoing monitoring**

Once the maintenance dose has been achieved and stable for 3 months consider monitoring FBC, creatinine/calculated GFR, albumin, ALT and/or AST at least every 12 weeks

### **Action required if abnormal results**

Withhold treatment until discussion with consultant specialist if<sup>1</sup>:

- WCC < 3.5 x 10<sup>9</sup>/L,
- Neutrophils < 1.6 x 10<sup>9</sup>/L
- Unexplained eosinophilia > 0.5x 10<sup>9</sup>/L
- Platelets < 140 x 10<sup>9</sup>/l,
- AST and/or ALT increase to >100units/ml
- Unexplained fall in serum albumin <30g/L
- MCV > 105f/L
- Creatinine increase > 30% above baseline over 12 months and/or calculated GFR < 60ml/min/1.73m<sup>2</sup>

### Additional notes

Physicians should ensure that women and men taking mycophenolate mofetil and mycophenolic acid understand: the risk of harm to a baby; the need for effective contraception; the need to plan for pregnancy and change treatment as necessary; and the need to immediately consult a physician if there is a possibility of pregnancy. Women should use 2 forms of effective contraception during treatment and for 6 weeks after stopping treatment. Men (including those who have had a vasectomy) should use condoms during treatment and for at least 90 days after stopping treatment. This advice is a precautionary measure due to the genotoxicity of these products. Female partners of male patients treated with mycophenolate mofetil or mycophenolic acid should use highly effective contraception during treatment and for 90 days after the last dose<sup>4</sup>

Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding.<sup>2</sup> If severe sore throat, abnormal bruising – withhold until FBC result is available and discuss with specialist team.<sup>3</sup>

Whilst absolute values are useful indicators, trends are equally important, and any rapid fall or consistent downward trend in any parameter warrants extra vigilance.<sup>3</sup>

If new or increasing dyspnoea or dry cough - withhold until discussed with specialist team.<sup>3</sup>

### References

1. BSR/BHPR non biologic (DMARD) guideline (2017)
2. BNF 66 (September 2013)
3. CKS: DMARDs - mycophenolate (Last revised in July 2015)
4. MHRA- Mycophenolate mofetil, mycophenolic acid: new pregnancy-prevention advice for women and men. Issued Dec 2015

## Nitrofurantoin (long-term)

### Tests prior to starting treatment

Contraindications for the use of nitrofurantoin include: <sup>1</sup>

- i) deficiency of glucose-6-phosphate dehydrogenase or acute porphyria<sup>1</sup>
- ii) acute porphyria<sup>1</sup>
- iii) eGFR <45 mL/minute/1.73 m<sup>2</sup> (as there is a risk of peripheral neuropathy and treatment may be ineffective due to inadequate urine concentrations) <sup>1, 2</sup>

Consider checking renal function, especially in the elderly <sup>3</sup>

Liver function <sup>4</sup>

### Monitoring until patient is stabilised

Renal function (no national recommendations available)

**Commented [A32]:** Frequency should be determined locally

Liver function <sup>4</sup>

**Commented [A33]:** Frequency should be determined locally

Monitor closely for pulmonary symptoms, especially in the elderly <sup>4</sup>

### Ongoing monitoring

Renal function (no national recommendations available)

**Commented [A34]:** Frequency should be determined locally

Liver function <sup>4</sup>

**Commented [A35]:** Frequency should be determined locally

Monitor closely for pulmonary symptoms, especially in the elderly <sup>4</sup>

### Action required if abnormal results

Treatment should be discontinued if the person develops unexplained pulmonary, hepatotoxic, haematological, or neurologic syndromes. <sup>1</sup>

### Additional notes

Advise patients to report any signs/symptoms suggestive of pulmonary toxicity (e.g. cough; chest pain; dyspnoea), hepatotoxicity, peripheral neuropathy (sensory as well as motor involvement) or haemolysis. <sup>1</sup>

Note that the onset of hepatotoxicity can be insidious and symptoms can be non-specific (e.g. nausea, rash, headache, flu-like symptoms). Cholestatic jaundice is generally associated with short-term therapy (usually up to two weeks) whereas chronic active hepatitis, occasionally leading to hepatic necrosis, is generally associated with long-term therapy (usually after six months). <sup>1</sup>

The severity of chronic pulmonary reactions and their degree of resolution appear to be related to the duration of therapy after the first clinical signs appear. It is therefore

important to recognise symptoms as early as possible. Note that minor symptoms such as fever, chills, cough and dyspnoea may be significant. Pulmonary function may be impaired permanently, even after cessation of therapy. <sup>1</sup>

People taking nitrofurantoin are susceptible to false positive urinary glucose (if tested for reducing substances) <sup>1</sup>

Urine may be coloured yellow or brown after taking nitrofurantoin. <sup>1</sup>

### References

1. Summary of Product Characteristics (SPC) for Nitrofurantoin 100mg Capsules (Concordia International; date of revision of text July 2014)
2. Clinical Knowledge Summaries. Urinary tract infection – lower (women). Last revised July 2015. Available at <https://cks.nice.org.uk/urinary-tract-infection-lower-women>
3. MHRA Drug Safety Update volume 8 issue 2, September 2014: A3. Available at <https://www.gov.uk/drug-safety-update/nitrofurantoin-now-contraindicated-in-most-patients-with-an-estimated-glomerular-filtration-rate-egfr-of-less-than-45-ml-min-1-73m2>
4. BNF July 2017. Accessed at <https://www.medicinescomplete.com/mc/bnf/current/>

## **NSAIDs (including COX II)**

### **Tests prior to starting treatment**

#### **For patients with ischaemic heart disease, risk factors for CVD, cerebrovascular disease, peripheral vascular disease and the elderly<sup>2</sup>:**

Consider BP, renal function (either creatinine clearance or eGFR) and features of heart failure

#### **For patients with heart failure<sup>2</sup>**

All NSAIDs are contra-indicated in patients with severe heart failure and diclofenac, aceclofenac, celecoxib, etoricoxib and high-dose ibuprofen (ie  $\geq 2.4\text{G/day}$ ) are contra-indicated in patients with established congestive heart failure (NYHA Class II-IV)<sup>3</sup>

Consider features of heart failure such as body weight, jugular venous distension, crepitations, hepatomegaly, ascites, peripheral oedema), renal function (either creatinine clearance or eGFR)

For patients with hypertension<sup>2</sup>

Consider BP

For patients with renal impairment<sup>2</sup>

Consider renal function (either creatinine clearance or eGFR)

Co-prescribe a proton pump inhibitor with NSAIDs for people who have osteoarthritis, rheumatoid arthritis or for people over 45 years who have low back pain in accordance with NICE guidance<sup>3</sup>.

### **Monitoring until patient is stabilised**

For patients with ischaemic heart disease, risk factors for CVD, cerebrovascular disease, peripheral vascular disease and the elderly<sup>2</sup>:

Consider checking BP 2-4 weeks (two weeks if using etoricoxib) after starting (or a dose increase), renal function (either creatinine clearance or eGFR) 1-2 weeks after starting (or a dose increase) and especially if also taking an ACEI or ARB. Also check for symptoms of heart failure

#### **For patients with heart failure<sup>2</sup>**

Assess features of heart failure such as body weight, jugular venous distension, crepitations, hepatomegaly, ascites, peripheral oedema) 1-2 weeks after starting treatment or increasing the dose, monitor renal function (either creatinine clearance or eGFR) 1-2 weeks after starting treatment or increasing the dose (particularly in patients taking an ACEI or ARB)

**For patients with hypertension<sup>2</sup>**

Monitor BP 2-4 weeks (2 weeks after starting etoricoxib) after starting treatment or increasing the dose

**For patients with renal impairment<sup>2</sup>**

Consider renal function (either creatinine clearance or eGFR)

**For patients with hepatic impairment**

As ask adverse effects as NSAIDs increase the riskof GI bleeding and fluid retention

**Ongoing monitoring**

No advice on monitoring any of the above parameters was identified

Commented [d36]: Local consensus needed

**Action required if abnormal results**

Review risks vs benefits in light of any changes in patient's baseline parameters.

**Additional notes**

NSAIDs should always be used at the lowest effective dose and for the shortest period of time to control symptoms and the need for long-term treatment should be reviewed periodically.<sup>1</sup>

Asthma: any degree of worsening of asthma may be related to the ingestion of NSAIDs, either prescribed or purchased over the counter.<sup>1</sup>

**References**

1. BNF accessed via Medicines Complete (December 2016)
2. CKS: NSAIDs prescribing issues. Last revised in July 2015
3. NICE Key Therapeutic Topics. Non-steroidal anti-inflammatory drugs. Published Jan 2015

## D-Penicillamine

### Tests prior to starting treatment

FBC including platelets  
urinalysis for proteinuria,  
U&Es and creatinine<sup>1,2,3</sup>

### Monitoring until patient is stabilised

Urinalysis for protein/ blood and FBC every 2 weeks until on a stable dose for 3 months<sup>1,3</sup>  
BNF recommends urinalysis for protein/ blood and FBC (including platelets) every 1 or 2 weeks for first 2 months and in the week after any dose increase<sup>2</sup>

### Ongoing monitoring

Urinalysis for protein/blood and FBC every 4 weeks<sup>2,3,4</sup>.

The BNF states that longer intervals may be adequate in cystinuria and Wilson's disease<sup>2</sup>

### Action required if abnormal results

Withhold treatment until discussion with rheumatologist if WBC<3.5, neutrophils<2.0, platelets<150<sup>1,3</sup>

BNF recommends consideration of withdrawal if WCC < 2.5 or platelets < 120 or there are 3 successive falls in count. Restart at reduced dose when counts return to within reference range but permanent withdrawal necessary if recurrence of leucopenia or thrombocytopenia<sup>2,4</sup>

If proteinuria is 2+ or more, check MSSU: If evidence of infection treat appropriately. If sterile and 2+ proteinuria or more persists (on two consecutive measurements), withhold until discussed with specialist team.<sup>1,3</sup>

If abnormal bruising or sore throat- withhold until FBC available<sup>1,3</sup>

### Additional notes

Ask patient about presence of rash or oral ulceration at each visit. If rash severe or oral ulceration present (late rashes more serious than early ones), withhold until discussed with specialist.<sup>1,3</sup>

Patients should be told to tell doctor immediately if sore throat, fever, infection, non-specific illness, unexpected bleeding and bruising, purpura, mouth ulcers, or rashes.<sup>2</sup>

Patients who are hypersensitive to penicillin may react rarely to penicillamine.<sup>2</sup>  
Longer intervals for blood counts and urine tests may be adequate in cystinuria.<sup>1,2,3</sup>

**Commented [ED37]:** Penicillamine was not addressed in the BSR 2017 update – therefore the recommendations cited here are taken from the 2008 version.

Alteration of taste may settle spontaneously. <sup>1,3</sup>  
Especially careful monitoring is necessary in the elderly since increased toxicity has been observed in this patient population regardless of renal function. <sup>4</sup>

## References

1. BSR/BHPR Guideline for disease modifying anti-rheumatic drug therapy (DMARD) in consultation with the British Association of Dermatologists (2008)
2. BNF. Accessed via MedicinesComplete (last updated August 2017)
3. CKS – DMARDs: Penicillamine Last revised July 2015
4. SPC for D-penicillamine (Distamine™ tablets). Last revised Jan 2014

**Commented [ED38]:** Penicillamine was not addressed as part of 2017 update – therefore recommendations cited here relate to those issued in this versionj

## **Phenytoin**

### **Tests prior to starting treatment**

The value of routine monitoring of FBC is questioned<sup>2,3,4</sup>. However NICE recommend that patients receiving an enzyme inducing medicine should have FBC, LFTs, U&Es and Vitamin D levels (and other test of bone metabolism such as calcium or ALP) assessed every 2-5 years so baseline values may be useful.

### **Monitoring until patient is stabilised**

SPC suggests frequent FBC throughout treatment<sup>1</sup> but BNF and SIGN state that evidence of practical value is uncertain<sup>3,4</sup>

Drug monitoring in patients with epilepsy should NOT be routinely performed unless to assess adherence, suspected toxicity, after adjustment of phenytoin dose, to manage a pharmacokinetic interaction or following onset of specific clinical conditions (eg pregnancy, organ failure, status epilepticus)<sup>2,4</sup>

Where monitoring is felt to be necessary, dosage should be adjusted according to serum levels where assay facilities exist.<sup>1</sup>

### **Ongoing monitoring**

SPC suggests frequent FBC throughout treatment<sup>1</sup> but BNF states that practical value is unsatisfactory<sup>3</sup>

NICE suggest that regular blood test monitoring is not recommended as routine however they do suggest FBC, U&Es, liver enzymes, Vitamin D levels, and other tests of bone metabolism every 2-5 years for adults taking enzyme-inducing drugs<sup>2</sup>

SIGN suggest that liver function and full blood count should not be monitored routinely and there is no indication for routine monitoring of drug levels<sup>4</sup>

Serum folate at least 6 monthly<sup>1</sup> but again this is not supported by NICE, SIGN or BNF.<sup>2,3,4</sup>

### **Action required if abnormal results**

Leucopenia, which is severe, progressive, or associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative)<sup>3</sup>

Asymptomatic minor abnormalities in test results are not necessarily an indication for changes in medication<sup>2</sup>

Folic acid supplements to be initiated where necessary.<sup>1</sup>

### **Additional notes**

Therapeutic serum level 10-20µg/ml although some cases of tonic clonic seizures may be controlled with lower serum levels<sup>1</sup>

Doctors and pharmacists should ensure that MHRA advice is followed and that patients are maintained on a specific manufacturer's version of phenytoin<sup>3</sup>

Phenytoin is highly protein bound and where protein binding is reduced, as in uraemia, total phenytoin levels will be reduced accordingly. Under these circumstances therapeutic control may be achieved with total phenytoin levels below the normal range. Patients with impaired liver function, elderly patients or those who are gravely ill may show early signs of toxicity<sup>1</sup>

Phenytoin may cause slight decrease in serum levels of total and free thyroxine, but levels of circulating TSH are not affected, therefore the latter can be used for diagnosis of hypothyroidism in a patient on phenytoin. <sup>1</sup>

Phenytoin may affect blood sugar metabolism tests<sup>1</sup> (no additional data provided)

Patients/carers should be told how to recognise signs of blood or skin disorders<sup>3</sup>.

### **References**

1 SPC for Phenytoin Sodium Flynn Hard Capsules 25mg, 50mg, 100mg and 300mg (revised Nov 2016)

2 NICE Clinical Guideline CG 137 (The epilepsies: diagnosis and management of the epilepsies in adults in primary and secondary care) (2012) (last updated Feb 2016)

3 BNF – accessed via Medicines Complete Dec 2016

4 SIGN Guideline No 143 – Diagnosis and management of epilepsy in adults (May 2015)

## Pioglitazone

### Tests prior to starting treatment

Contraindications for the use of pioglitazone include: <sup>1,2</sup>

- cardiac failure or a history of cardiac failure (NYHA stages I to IV)
- current bladder cancer or a history of bladder cancer
- uninvestigated macroscopic haematuria

The DTB recommends that use should probably be avoided in women at high risk of fractures <sup>3</sup>

Liver function: LFTs<sup>1,2</sup>.

Weight <sup>1</sup>

FBC<sup>5</sup>

### Monitoring until patient is stabilised

LFTs should be monitored periodically based on clinical judgement<sup>1,2,5</sup>

### Ongoing monitoring

LFTs should be monitored periodically based on clinical judgement and must be checked if patient develops signs suggesting liver dysfunction<sup>1,2</sup>.

Patients should be observed for signs and symptoms of heart failure, weight gain or oedema; particularly those with reduced cardiac reserve<sup>1,5</sup>

### Action required if abnormal results

Do not initiate therapy if ALT > 2.5 X upper limit of normal or if there is any other evidence of liver disease<sup>5</sup>

The risk of anaemia is increased if Hb is low before starting treatment<sup>5</sup>

Investigate any macroscopic haematuria before starting pioglitazone therapy<sup>1</sup>

If ALT levels are increased to 3 X upper limit of normal during therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 X the upper limit of normal, therapy should be discontinued.<sup>1,2,5</sup>

If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with pioglitazone should be guided by clinical judgement pending laboratory evaluations <sup>1,5</sup>

If jaundice is observed therapy should be discontinued. <sup>1,5</sup>

**Commented [d39]:** In the absence of clear national guidance a local guideline may be needed e.g. monitor LFTs at least annually or more frequently if there are concerns about liver impairment.

### **Additional notes**

Advise patients to seek immediate medical attention if symptoms such as nausea, vomiting, abdominal pain, fatigue and dark urine develop<sup>3</sup>

The risk of weight gain, heart failure and peripheral oedema is increased when pioglitazone is used in combination with insulin

Advise patients to promptly seek medical attention if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.

Thiazolidinediones, including pioglitazone have been associated with decreased visual acuity due to worsening or new onset macular oedema. If patients report disturbances in visual acuity ophthalmological referral should be considered <sup>1,2</sup>

To mitigate against the bladder cancer risks, the MHRA advises that the safety and efficacy of pioglitazone should be reviewed after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated <sup>4,5</sup>.

### **References**

1. Summary of Product Characteristics (SPC) for Actos (date of revision of text May 2016),
2. BNF: accessed via Medicines Complete December 2016
3. DTB Vol 46 No 4 April 2008:25-29
4. MHRA Drug Safety Update, August 2011, available at: <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON125962>
5. CKS Diabetes Type 2 - pioglitazone. Last revised July 2016

## Propylthiouracil

### Tests prior to starting treatment

Specialist Initiation only<sup>1,9</sup>

TFTs (TSH and FT4)<sup>1,3,9</sup>

LFTs<sup>9</sup>

renal function (eGFR)<sup>9</sup>

WBC (incl differential)<sup>4,9</sup>

### Monitoring until patient is stabilised

UK Guidelines recommend TFTs every 1-3 months until stable<sup>3</sup>. CKS recommend TSH and FT4 every 4–6 weeks for the first few months, to allow the specialist to adjust drug doses and to avoid iatrogenic hypothyroidism<sup>9</sup>

Monitor for signs and symptoms of liver injury, especially during the first 6 months after initiation of therapy<sup>8</sup>.

### Ongoing Monitoring

Monitor TFTs every 3 months once on maintenance treatment after dose titration. If using a “block and treat” regimen monitor TFTs after 3 months and then every 6 months.<sup>9</sup>

UK Guidelines recommend annual TFT monitoring once stable if being used as a long-term treatment option<sup>3</sup>

**Commented [d40]:** Local consensus needed on which of these two approaches is accepted locally

### Action required if abnormal results

Repeat WBC if patient develops fever, mouth ulcers, sore throat or other symptoms of infection<sup>4</sup>

Stop drug and recommend immediate specialist referral if leucocyte count falls to  $<1.5 \times 10^9/L$  or neutrophil count to  $<0.5 \times 10^9/L$ <sup>4</sup>

Discontinue drug and repeat LFTs if patient develops pruritic rash, jaundice, light coloured stool or dark urine, joint pain, abdominal pain or bloating, anorexia, nausea, or fatigue.<sup>6</sup> Provide supportive care<sup>8</sup>.

Renal impairment — three-quarters of the normal dose should be used if the estimated glomerular filtration rate (eGFR) is 10–50 mL/min/1.73m<sup>2</sup>; half the normal dose should be used if the eGFR is less than 10 mL/min/1.73m<sup>2</sup>.<sup>9</sup>

### Additional notes

Patients should be made aware that the development of certain adverse effects (fever, mouth ulcers, rashes, sore throat) may be an indication of agranulocytosis, a serious reaction to the drug, and they should contact their doctor immediately as treatment should be stopped. A full blood count should be performed if there is clinical evidence of infection<sup>2</sup>

Patients should also be made aware that the development of certain adverse effects (jaundice, fatigue, malaise, nausea, anorexia) may be an indication of hepatotoxicity, and they should contact their doctor immediately as treatment should be stopped.

### References

1. Consensus statement for good practice and audit measures in management of hypothyroidism & hyperthyroidism BMJ 1996; 313:539–544
2. Summary of Product Characteristics for propylthiouracil. Date of revision of text, January 2011
3. UK Guidelines for thyroid function tests by Assoc. Clinical Biochemistry, British Thyroid Assoc and British Thyroid Foundation (July 2006)
4. Best practice in primary care pathology: review 4. J Clin Pathol 2006; 59: 893-902
5. Cooper DS and Rivkees SA. Putting propylthiouracil in perspective. Journal of clinical endocrinology and metabolism. 2009; 94(6). DOI <http://dx.doi.org/10.1210/jc.2009-0850>
6. Bahn HS et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Endocrine practice. 2011; 17(3):456–520
7. BNF – accessed via Medicines Complete December 2016
8. FDA Alert. Information for healthcare professionals – propylthiouracil-induced liver failure. April 2009. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm162701.htm>
9. Clinical Knowledge Summaries. Hyperthyroidism. Scenario: Management:. Last revised June 2016. Available at <https://cks.nice.org.uk/hyperthyroidism#!prescribinginfosub>

## Rivaroxaban

### Tests prior to starting treatment

Clotting screen

renal function tests/ creatinine clearance, LFTs, FBC<sup>2</sup>  
BP<sup>6</sup>

### Monitoring until patient is stabilised

Ideally assess every 3 months to:

- Assess compliance and reinforce advice regarding regular dosing schedule.
- Enquire about adverse effects such as bleeding.
- Assess for the presence of thromboembolic events
- Enquire about other medicines, including OTC medicines. <sup>2</sup>

### Ongoing Monitoring

Renal function tests, FBC at least once a year. <sup>2</sup>

Repeat renal function tests every 6 months if CrCl 30–60 mL/min or every 3 months if CrCl 15–30 mL/min. <sup>2</sup>

More frequent renal function tests/LFTs advised if intercurrent illness that may impact renal or hepatic function. <sup>2</sup>

### Action required if abnormal results

If renal function has declined, review treatment, as rivaroxaban may need to be stopped or a lower dose may be required. <sup>2</sup>

If the patient's HASBLED score is more than 3, then the patient is at a high risk of bleeding rivaroxaban should be used cautiously, with regular reviews.<sup>4</sup>

If there is an unexplained fall in haemoglobin and/or haematocrit, occult bleeding may be present. <sup>2</sup>

### Additional notes

The MHRA has advised that because of the significant risk of major bleeding, special care should be taken in patients with co morbidities, procedures and concomitant treatments and attention should be paid to renal function. <sup>3</sup>

Recently issued guidance from UKCPA recommends that rivaroxaban should be stopped at least 2 days (ie 1 dose) before a procedure with a low bleeding risk and at least 3 days (ie 2 doses) before a procedure with a high bleeding risk. Longer periods are recommended in patients with impaired renal function. No rivaroxaban should be taken on the day of the procedure. <sup>6</sup>

**Commented [ED41]:** Renal function should be based on Cockcroft Gault calculation – a local protocol on guidance in extremes of body weight is advisable. SE London Guidance is available: <http://www.lambethccg.nhs.uk/news-and-publications/meeting-papers/south-east-london-area-prescribing-committee/Documents/Cardiovascular%20Disease%20Guidelines/Creatinine%20clearance%20guidance%20July%202017.pdf>

**Commented [d42]:** Needed in conjunction with renal function and liver function if want to calculate HAS-BLED score

**Commented [ED43]:** See comment above regarding assessment of renal function

## References

1. BNF accessed via Medicines Complete Feb 2017
2. CKS: Anticoagulation – oral. Dec 2016
3. MHRA guidance. Drug Safety Update 2013; 7/3
4. HAS-BLED score for bleeding risk on oral anticoagulation in atrial fibrillation (AF). Accessed via:  
<http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20110126115649933383>  
on 1/3/2017
5. SPC for rivaroxaban – last updated May 2015
6. UKCPA Handbook of per-operative medicines. Published Oct 2016

## **Sirolimus**

### **Tests prior to starting treatment**

Renal function (serum creatinine), liver function, lipid levels and BP <sup>1,2,6</sup>

Consider NICE recommendations regarding screening for HIV and hepatitis B and C in patients at increased risk of infection <sup>3</sup>

### **Monitoring until patient is stabilised**

Blood levels: when used with ciclosporin (for the initial 2-3 months post-transplantation), the trough whole blood sirolimus concentration (chromatographic assay) should be 4-12mcg/L (local treatment protocols may differ).<sup>1,2,6</sup> The first sample should be taken about 4 days or more after the initial loading dose, and then weekly for the first month and every 2 weeks for the second month.<sup>4</sup> Therapeutic drug monitoring is also necessary after changes in the dose of sirolimus or ciclosporin, or of their relative timing. <sup>4,5</sup>.

When concomitant ciclosporin is discontinued, the sirolimus dose should be adjusted to maintain the trough whole blood sirolimus concentration (chromatographic assay) at 12-20mcg/L (local treatment protocols may differ) <sup>1,2</sup>

Dose adjustments should ideally be based on more than a single trough level obtained more than 5 days after a previous dosing change.<sup>1</sup>

Sirolimus whole blood concentration should be monitored 1–2 weeks after changing between oral solution and tablets.<sup>2</sup>

Renal function: renal function (including urine proteins) should be monitored, especially when given with ciclosporin.<sup>2</sup>

### **Ongoing Monitoring**

#### Renal function

Renal function (including urine proteins) should be monitored, especially when given with ciclosporin.<sup>2</sup>

The UK Renal Association recommends that renal transplant recipients have their renal function (serum creatinine and urine protein excretion) recorded at each clinic visit.<sup>6</sup>

They recommend that for the first three months after transplant patients are seen a few times weekly but if uncomplicated from 3 months onwards patients should be seen in clinic every 2-4 weeks, from 6 months onwards every 4-6 weeks and from 12 months onwards every 3-6 months.

#### Blood pressure

The UK Renal Association recommends that renal transplant recipients have their blood pressure recorded at each clinic visit.<sup>6</sup> (clinic frequency described above)

#### Lipid levels

The BNF advises monitoring lipids<sup>2</sup>; the UK Renal Association recommends that a fasting lipid level is done on an annual basis in all renal transplant recipients.<sup>6</sup>

### Diabetes

Dipstick urinalysis and blood sugar level should be measured at each renal transplant clinic visit to check for the development of new onset diabetes after transplantation.<sup>6</sup> Clinic frequency is described above.

### Vaccination

The UK Renal Association recommends that patients should have hepatitis B surface antibody (HBsAb) levels rechecked annually and be revaccinated if antibody titres fall below 10 mIU/mL. Patients should not receive live attenuated vaccines but should receive annual flu vaccine (unless contraindicated) and a pneumococcal vaccine and a booster every five years.

### **Action required if abnormal results**

In severe hepatic impairment, decrease dose by 50% and monitor whole blood-sirolimus trough concentration every 5–7 days after any dose adjustment or loading dose, until 3 consecutive measurements have shown stable blood-sirolimus concentration.<sup>1,2</sup>

Appropriate adjustment of the immunosuppression regimen should be considered in patients with elevated serum creatinine levels.<sup>1</sup>

Hypertension – a blood pressure of > 140/90 mmHg in clinic (130/80 mmHg if PCR >50 or ACR > 35) should be followed up and treated according to local protocol.<sup>6</sup>

If hyperlipidaemia is detected, subsequent interventions such as diet, exercise, and lipid-lowering agents should be initiated.<sup>1</sup> Treatment targets should be the same as in the general population.<sup>5</sup> In patients with severe refractory hyperlipidaemia, the risk/benefit of continued sirolimus therapy should be re-evaluated.<sup>1</sup>

New onset diabetes after transplant should be managed according to local unit protocol.<sup>6</sup>

### **Additional notes**

Exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.<sup>1</sup> The UK Renal Association recommends use of total sunblock (SPF ≥ 50) and advises annual skin examination by a trained healthcare professional.<sup>6</sup>

### **References**

1. Summary of Product Characteristics for sirolimus (Rapamune). Date of revision of text July 2016.
2. BNF accessed via Medicine Complete February 2017

3. NICE public health guidance 43: Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (2012). Available: <https://www.nice.org.uk/guidance/ph43>
4. Stenton SB, et al. [Sirolimus: the evidence for clinical pharmacokinetic monitoring](#). Clin Pharmacokinet 2005; 44: 769–86.
5. Oellerich M, Armstrong VW. [The role of therapeutic drug monitoring in individualizing immunosuppressive drug therapy: recent developments](#). Ther Drug Monit 2006; 28: 720–5. [PubMed](#)
- 6 UK Renal Association (2017) Post-operative Care of the Kidney Transplant Recipient –available: <http://www.renal.org/docs/default-source/guidelines-resources/post-operative-care-in-the-kidney-transplant-recipient.pdf?sfvrsn=0#page=73&zoom=auto,-82,409>

## **Spirolactone (adjunct in moderate to severe heart failure)**

### **Tests prior to starting treatment**

U&Es (including creatinine) and eGFR<sup>1,2</sup>

### **Monitoring until patient is stabilised**

In patients with moderate to severe heart failure (NYHA class II-IV) U&Es (including creatinine) and eGFR at 1 week after initiation or increase in dose of spironolactone, then at one, four, eight and 12 weeks; then six, nine and 12 months; and 4- monthly<sup>3</sup> or 6-monthly<sup>1,2,4</sup> thereafter.

If other drugs that can cause renal failure or hyperkalaemia are started in a patient already established on spironolactone, this should be monitored in the same way as an increase in dose of spironolactone.

### **Ongoing monitoring**

U&Es (including Creatinine) and eGFR 4- monthly<sup>3</sup> or 6-monthly<sup>1,2,4</sup>

### **Action required if abnormal results**

Spirolactone should not be started in patients with serum potassium  $\geq 5.0$  mEq/L<sup>1,4</sup> and serum creatinine  $\geq 2.5$  mg/dL<sup>1</sup> (serum creatinine  $>220$  micromol/L or CKD stage 3 [eGFR  $< 30$  mL/min/1.73m<sup>2</sup>]<sup>3,4</sup>

The manufacturer advises that in patients with severe heart failure discontinue or interrupt treatment for serum potassium  $>5$  mEq/L or for serum creatinine  $>4$  mg/dL<sup>1</sup>.

### **NICE guidance<sup>2</sup>**

- Halve the aldosterone antagonist dose if the potassium rises to 5.5-5.9 mmol/L.
- Stop the aldosterone antagonist if the potassium rises above 6 mmol/L or the creatinine above 220 micromol/L".

### **SIGN guidance<sup>4</sup>**

- If serum potassium rises above 5.5 mmol/L or creatinine rises to  $>220$  micromol/L reduce the dose to 25mg on alternate days and monitor blood chemistry closely.
- If potassium rises  $\geq 6$  mmol/L or creatinine to 310 micromol/L, stop spironolactone immediately and seek specialist advice.

### **ESC guidance<sup>3</sup>**

- If potassium rises above 5.5 mmol/L or creatinine rises to 221 micromol/L or eGFR  $< 30$  mL/min/1.73m<sup>2</sup>, halve dose and monitor blood chemistry closely.
- If potassium rises to  $>6$  mmol/L or creatinine to  $>310$  micromol or eGFR  $< 20$  mL/min/1.73m<sup>2</sup> stop spironolactone immediately and seek specialist advice.

## Additional notes

Advise patients to avoid NSAIDs not prescribed by a physician and salt substitutes high in potassium. If diarrhoea and/or vomiting occurs<sup>3,4</sup> or there is infection with fever leading to intense sweating<sup>3</sup>, patients should be aware of the risk of dehydration and electrolyte imbalance and contact their physician/specialist nurse<sup>3,4</sup>. SIGN guidance advises patients to stop the spironolactone and contact their physician<sup>4</sup>. The MHRA has issued a warning that "concomitant use of spironolactone with ACE inhibitors or angiotensin-II receptor antagonists increases the risk of severe hyperkalaemia, particularly in patients with marked renal impairment, and should be used with caution<sup>5,6</sup>." The report describes a case of fatal hyperkalaemia in a patient with heart failure, diabetes, and chronic renal failure who was being treated with several medicines including spironolactone. A low-dose ACE inhibitor was subsequently added for treatment of increased blood pressure. A few days later, the patient was admitted to hospital with severe hyperkalaemia and acute-on-chronic renal failure and subsequently died<sup>5</sup>.

## References

1. Pfizer Limited. Summary of Product Characteristics Aldactone 100 mg tablets. Last Updated 04-Apr-2016. Accessed via <http://www.medicines.org.uk/emc/medicine/27264> on 30/06/16
2. National Institute for Health and Care Excellence. NICE clinical guideline 108. Chronic heart failure in adults: management. Appendix D Practical Notes. Published 25 August 2010. Accessed via <https://www.nice.org.uk/guidance/cg108/chapter/1Guidance#treating-heart-failure> on 30/06/16
3. The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal* 2016; 37: 2129–2200 and Web Addenda doi:10.1093/eurheartj/ehw128 accessed via <http://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-and-Chronic-Heart-Failure> on 27/01/17
4. Scottish Intercollegiate Guideline Network SIGN 147 • Management of chronic heart failure. A national clinical guideline March 2016. Annex 5. Accessed via <http://www.sign.ac.uk/pdf/SIGN147.pdf> on 29/06/16
5. Medicines and Healthcare products Regulatory Agency. Spironolactone and renin-angiotensin system drugs in heart failure: risk of potentially fatal hyperkalaemia. Drug Safety Update volume 9 issue 6 February 2016: 2. Accessed via <https://www.gov.uk/drug-safety-update/spironolactone-and-renin-angiotensin-system-drugs-in-heart-failure-risk-of-potentially-fatal-hyperkalaemia#reporting-of-cases-of-hyperkalaemia> on 22/07/16
6. Medicines and Healthcare products Regulatory Agency. Spironolactone and renin-angiotensin system drugs in heart failure: risk of potentially fatal hyperkalaemia—clarification. Drug Safety Update 2016; 10 (5): 2 [online]. Available: <https://www.gov.uk/drug-safety-update/spironolactone-and-renin-angiotensin-system-drugs-in-heart-failure-risk-of-potentially-fatal-hyperkalaemia-clarification>
7. BNF July 2016. Accessed via <http://www.evidence.nhs.uk/formulary/bnf/current> on 22/07/2016

## Statins

### Tests prior to starting treatment

Baseline full lipid profile least one sample taken to measure total cholesterol, non-HDL cholesterol, HDL cholesterol and triglycerides. <sup>1,3</sup>. This does NOT need to be a fasting sample<sup>1,3</sup>

Transaminase level (ALT or AST) <sup>1,3</sup>

Renal function and eGFR <sup>1,3</sup>

Thyroid-stimulating hormone<sup>1,3</sup>

HbA<sub>1c</sub><sup>1,3</sup>

BP <sup>1,3</sup>

BMI or other measure of obesity<sup>1,3</sup>

Creatine kinase level (only if patient has persistent generalised unexplained muscle pain)

### Monitoring until patient is stabilised

If patient on a high intensity statin (ie atorvastatin  $\geq$  20mg daily, rosuvastatin  $\geq$  10mg daily, or simvastatin 80mg daily) measure total cholesterol, HDL cholesterol and non-HDL cholesterol at 3 months.<sup>1,3</sup>

Measure transaminase levels (ALT or AST) at 3 months<sup>1,3</sup>

Ask patient if they are experiencing muscle symptoms (pain, tenderness, weakness) and if so measure creatine kinase<sup>1,3</sup>

HbA<sub>1c</sub> for fasting blood glucose should be repeated at 3 months if considered to be at risk of diabetes mellitus (BNF)

### Ongoing monitoring

Consider performing a non-fasting blood test for non-HDL cholesterol to help inform discussions at each annual medication review

**Commented [d44]:** Local guidance on strength of this recommendation may be needed to support practice.

Measure transaminase levels (ALT or AST) at 12 months but not again unless clinically indicated

Ask patient if they are experiencing muscle symptoms (pain, tenderness, weakness) and if so measure creatine kinase<sup>1,3</sup> However if they have previously tolerated statin therapy for more than 3 months explore other possible causes for symptoms and raised creatine kinase.

### Action required if abnormal results

Statin therapy should not be started/ discontinued if ALT or AST  $>$ 3x upper limit of normal (ULN) <sup>1,3</sup>.

If creatine kinase levels are more than 5 times the upper limit of normal, statin therapy should not be started/ discontinued and re-measured after 7 days. If levels are still 5

times the upper limit of normal do not start/ re-start. If levels are raised but less than 5 times the upper limit of normal, start statin treatment at a lower dose.

If eGFR is less than 30ml/min/1.73m<sup>2</sup> check appropriateness of dosing of statin with a renal specialist.

Rosuvastatin is contra-indicated if creatinine clearance <30ml/min Maximum 40mg dose if less than 60ml/min<sup>4</sup>

Patients with hypothyroidism should receive adequate replacement therapy before assessing their requirement for lipid-regulating treatment because correction may resolve the lipid abnormality and untreated hypothyroidism increases the risk of myositis.<sup>2</sup>

The British Thyroid Assoc. advise that in patients with subclinical hypothyroidism and TSH > 10mU/L there is an increasing evidence of progression to overt hypothyroidism and deterioration in hyperlipidaemia particularly in patients with elevated TPOab. There is evidence of improvement in lipid profile and symptoms when patients with modestly raised TSH were rendered euthyroid with thyroxine<sup>5</sup>

#### **Additional notes**

Patients should be advised to report unexplained muscle pain.<sup>1,2</sup>

#### **References**

1. NICE. Clinical Guideline (CG 181). Cardiovascular disease: risk assessment and reduction, including lipid modification. Published Jul 2014. Available: <https://www.nice.org.uk/guidance/cg181>
2. BNF. Accessed via Medicines Complete February 2017.
3. CKS. Lipid modification - CVD prevention. Last updated Sept 2015.
4. SPC for Crestor 5mg, 10mg, 20mg and 40mg film-coated tablets. Last updated Dec 2016. Available: <http://www.medicines.org.uk/emc/medicine/11976>
5. British Thyroid Association. (July 2006). *UK Guidelines for the Use of Thyroid Function Tests*. Available: [http://www.british-thyroid-association.org/info-for-patients/Docs/TFT\\_guideline\\_final\\_version\\_July\\_2006.pdf](http://www.british-thyroid-association.org/info-for-patients/Docs/TFT_guideline_final_version_July_2006.pdf).

## Sulfasalazine

### Tests prior to starting treatment

Renal function. <sup>1,2,5,6</sup> (BSR recommend creatinine/ calculated GFR)  
FBC <sup>1,2,5,6</sup>  
LFT <sup>2,5,6</sup> (BSR recommend ALT and/or AST and serum albumin)  
U&Es. <sup>5,6</sup>

BSR recommend that all patients starting DMARDs should have baseline measurement of height, weight and BP<sup>1</sup>

BSR state that:

There is a strong rationale for screening for hepatitis B and C in patients at increased risk of infection <sup>1</sup>

Baseline HIV status should also be established in those with risk factors <sup>1</sup>

Screening for lung disease should be undertaken at clinical discretion on a case-by-case basis.<sup>1</sup>

### Monitoring until patient is stabilised

#### IN GENERAL

BNF advises close monitoring of full blood counts (including differential white cell count and platelet count) and LFTs at monthly intervals during the first 3 months. They also note that although the manufacturer recommends renal function tests in rheumatic diseases, evidence of practical value is unsatisfactory – they recommend that renal function is assessed at 3 months<sup>1</sup>

#### IN RHEUMATOLOGY

FBC, creatinine/calculated GFR, ALT and/or AST, albumin every two weeks until dose stable for at least 6 weeks then monthly thereafter for 3 months. More frequent monitoring may be required in high-risk patients.<sup>1</sup>

Following a change in dose repeat FBC and LFTs, ALT and/or AST, creatinine/calculated GFR and albumin every 2 weeks until dose stable for 6 weeks and then revert to previous schedule<sup>1</sup>

### Ongoing monitoring

#### IN GENERAL

BNF suggests that renal function should be monitored annually<sup>1</sup>

#### IN RHEUMATOLOGY

Once the maintenance dose has been achieved and stable for 3 months consider monitoring FBC, creatinine/calculated GFR, albumin, ALT and/or AST and LFTs at least every 12 weeks. More frequent monitoring is appropriate in patients at higher risk of toxicity.<sup>6</sup>

BSR state that no routine monitoring is required in patients that have been stable on sulfasalazine for 12 months.<sup>6</sup>

**Commented [ED45]:** Local decision needed on whether to follow general advice or specific advice from BSR

**Commented [ED46]:** Local decision needed on whether to follow general advice or specific advice from BSR

**Action required if abnormal results**

Withhold treatment until discussion with consultant specialist if<sup>6</sup>:

WCC < 3.5 x 10<sup>9</sup>/L,

Neutrophils < 1.6 x 10<sup>9</sup>/L

Unexplained eosinophilia > 0.5x 10<sup>9</sup>/L

Platelets < 140 150 x 10<sup>9</sup>/l,

AST and/or ALT increase to > twice the upper limit of normal increase to >100units/ml

Unexplained fall in serum albumin <30g/L

MCV > 105f/L

Creatinine increase > 30% above baseline over 12 months and/or calculated GFR < 60ml/min/1.73m<sup>2</sup>

**Additional notes**

Advise patients to report any unexplained bleeding, bruising, sore throat, fever, or malaise. Perform a full blood count and stop treatment immediately if a blood dyscrasia or toxicity is suspected.<sup>1,2,3</sup> Ask about the presence of rash or oral ulceration at each visit.<sup>3</sup>

**References**

1. British National Formulary. Accessed via: <http://www.medicinescomplete.com> on 07/12/2016.
2. Summary of Product Characteristics for Salazopyrin tablets (sulfasalazine). Last updated on the eMC 25/02/2014. Accessed via: <https://www.medicines.org.uk/emc/medicine/10722> on 07/12/2016.
3. CKS July 2015. Ulcerative colitis. and DMARD- sulfasalazine. Accessed via: <http://cks.nice.org.uk/> on 07/12/2016.
4. BSG Guidelines for the management of inflammatory bowel disease in adults (2011). Accessed via: [http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/ibd/ibd\\_2011.pdf](http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/ibd/ibd_2011.pdf) on 07/12/2016.
5. Bath Clinical Area Partnership Prescribing and Therapeutics Committee. Summary of Shared Care Guidelines and Monitoring of Disease Modifying Drugs (DMARDs) Updated May 2016. Accessed via: [http://www.bcapformulary.nhs.uk/includes/documents/BCAP-Shared-Care\\_DMARD\\_monitoring\\_guidelines-May-2016-Final.pdf](http://www.bcapformulary.nhs.uk/includes/documents/BCAP-Shared-Care_DMARD_monitoring_guidelines-May-2016-Final.pdf) on 07/12/2016.
6. BSR/BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Published 2017.

## Tacrolimus

### Tests prior to starting treatment

ECG (for hypertrophic changes), BP, fasting blood glucose, U&Es (particularly potassium), liver and renal function tests, FBC, blood clotting values, plasma protein.<sup>1,2</sup>

Consider NICE recommendations regarding screening for HIV, hepatitis B and C in patients at increased risk of infection<sup>3</sup>

### Monitoring until patient is stabilised

#### Renal transplant

Blood levels: Whole blood trough levels (drawn approximately 12 hours post-dose, just prior to the next dose) should be monitored 3 times weekly during the early post-transplant period.<sup>1,4</sup> Clinical study analysis suggests that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20ng/ml.<sup>1</sup>

ECG: patients should be monitored by ECG pre- and post-transplant (e.g. initially at three months and then at 9-12 months) for hypertrophic changes.<sup>1</sup>

Monitoring of the following parameters should also be undertaken on a routine basis: BP, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein.<sup>1,2</sup>

#### Dermatology

No specific guidance was identified relating to the monitoring of patients receiving systemic tacrolimus for eczema

**Commented [d47]:** If this is to be monitored by non-specialists locally agreed guidance will be needed which may be based on BNF and post renal transplant guidance highlighted above

### Ongoing Monitoring

Blood levels: Whole blood trough levels should be monitored periodically during maintenance therapy<sup>2</sup>

Levels should be checked when any medication with possible interactions is prescribed, the dose or formulation is changed, or when there is unexplained graft dysfunction.<sup>4</sup>

#### Renal function

Weekly but if uncomplicated from 3 months onwards patients should be seen in clinic every 2-4 weeks, from 6 months onwards every 4-6 weeks and from 12 months onwards every 3-6 months.

#### Blood pressure

The UK Renal Association recommends that renal transplant recipients have their blood pressure recorded at each clinic visit.<sup>4</sup> (clinic frequency described above)

### Lipid levels

The BNF advises monitoring lipids<sup>2</sup>; the UK Renal Association recommends that a fasting lipid level is done on an annual basis in all renal transplant recipients.<sup>4</sup>

### Diabetes

Dipstick urinalysis and blood sugar level should be measured at each renal transplant clinic visit to check for the development of new onset diabetes after transplantation.<sup>4</sup> . Clinic frequency is described above.

### Vaccination

The UK Renal Association recommends that patients should have hepatitis B surface antibody (HBsAb) levels rechecked annually and be revaccinated if antibody titres fall below 10 mIU/mL. Patients should not receive live attenuated vaccines but should receive annual flu vaccine (unless contraindicated) and a pneumococcal vaccine and a booster every five years.

### **Action required if abnormal results**

If hypertrophic changes occur, consider dose reduction or discontinuation.<sup>1,2</sup>

New-onset diabetes after transplant should be managed according to local unit protocol.<sup>4</sup>

Lower doses and close monitoring of blood concentrations may be required in patients with severe hepatic impairment (Child-Pugh score of 10 or higher) because of reduced clearance and prolonged half-life<sup>6</sup>

### **Additional notes**

Patients should be informed that tacrolimus can cause diabetes and should be advised to see their clinician if they develop signs of high blood sugar like confusion, feeling sleepy, more thirst, more hungry, passing urine more often, flushing, fast breathing, or breath that smells like fruit..<sup>6</sup>

Excessive exposure to UV and sunlight should be avoided.<sup>2</sup> The UK Renal Association recommend covering the skin and use of total sunblock (SPF $\geq$ 50) and advise annual skin examination by a trained healthcare professional.<sup>4</sup>

Oral tacrolimus medicines should be prescribed and dispensed by brand name only.<sup>5</sup> Any switching between brands requires careful supervision and therapeutic monitoring by an appropriate specialist.<sup>2</sup>

### **References**

1. Summary Product Characteristics for tacrolimus (Adoport). Date of revision of text, Jan 2016
2. BNF accessed via Medicines Complete – February 2017
3. NICE public health guidance 43: Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (2012)
4. UK Renal Association (2017) Post-operative Care of the Kidney Transplant Recipient –available: <http://www.renal.org/docs/default-source/guidelines-resources/post-operative-care-in-the-kidney-transplant-recipient.pdf?sfvrsn=0#page=73&zoom=auto,-82,409>
5. MHRA : Updated Commission on Human Medicines recommendation for prescribing and dispensing of all oral tacrolimus products  
<http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON152758>
6. UpToDate Tacrolimus (systemic): Patient drug information accessed March 2017

## **Theophylline/ aminophylline**

### **Tests prior to starting treatment**

U&Es (paying particular attention to potassium)<sup>2,3,5</sup>  
LFTs<sup>2,3,5</sup>

Enquire about smoking status for patient, and advise patient to seek advice from doctor if status is likely to change<sup>1</sup>.

### **Monitoring until patient is stabilised**

It is advisable to recheck the plasma level after dose adjustment (at least 3 days after dose adjustment or 5 days after starting oral treatment for the first time)<sup>4</sup>  
Levels should be taken 4-6 hours after MR dose, at least 5 days after starting treatment and at least 3 days after dose adjustment. Sampling times may vary- consult local guidelines.<sup>4</sup>

### **Ongoing monitoring**

It is advisable to recheck plasma levels every 6-12 months. Check more regularly in older people or those with heart failure or hepatic impairment.<sup>5</sup>

Also check plasma theophylline levels if-

- If the person experiences side effects that may suggest toxicity (nausea, vomiting, tremor or palpitations)<sup>5</sup>
- If an enzyme-inhibiting drug (such as erythromycin, clarithromycin, allopurinol, or cimetidine) is prescribed (raises plasma levels) or if an enzyme-inducing drug (such as carbamazepine, rifampicin, or St John's Wort) is prescribed (lowers plasma levels)<sup>5</sup>
- If the person starts or stops smoking — a dose adjustment may be needed because tobacco can lower the plasma levels of theophylline.

Check potassium levels: periodically in at risk patients<sup>2,3,5</sup>

People taking theophylline alongside beta-2 agonists, corticosteroids, or diuretics, and in all people with severe asthma. Plasma potassium concentrations may be reduced by beta-2 agonists, corticosteroids, and diuretics. This effect may be potentiated by theophylline, and further exacerbated by hypoxia.

Monitor alcohol consumption as high levels of consumption can reduce plasma concentration of theophylline.<sup>2,3</sup>

### **Action required if abnormal results**

A lower dose may be required in patients with reduced hepatic function<sup>2,3</sup>

### **Additional notes**

In most individuals a plasma theophylline of between 10-20mg/ litre is required for satisfactory bronchodilation although a plasma theophylline concentration of 10mg/litre (or less) may be effective. Adverse effects can occur within the range 10-20mg/ litre and both the frequency and severity increase at concentrations above 20mg/ litre<sup>4</sup>

BTS/SIGN advise checking levels during pregnancy as protein binding decreases, the free level of drug will increase and so a lower therapeutic range is probably appropriate. They particularly recommend checking levels in pregnant women with acute severe asthma and in those that are critically dependent on therapeutic theophylline levels.<sup>6</sup>

## References

1. Medicines and Healthcare products Regulatory Agency. Drug Safety Update: Volume 3, Issue 3, October 2009. [Available from <https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency>]
2. Summary of Product Characteristics. Nuelin SA – Meda Pharmaceuticals. Date of revision of the text: Sept 2016.
3. Summary of Product Characteristics. Phyllocontin Continus. Date of revision of the text: Jan 2014.
4. BNF accessed via Medicines Complete February 2017
5. Clinical Knowledge Summaries – Asthma. Last updated December 2016. Accessed online via <https://cks.nice.org.uk/asthma#!prescribinginfosub:16/>
6. British Thoracic Society/ SIGN. British Guideline on the management of asthma (revised Sept 2016). Accessed online via <https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2016/>

## **Thyroxine (levothyroxine)**

### **Tests prior to starting treatment**

TFTs.<sup>1,2</sup> (UK guidance recommend TSH and FT4 as most important markers<sup>2</sup>)  
ECG<sup>1,3,4</sup>

Consensus guidance recommends that patients with hypothyroidism only need referral in the following circumstances: age < 16 yrs, pregnant or post partum, evidence of pituitary disease, newborn infant.<sup>5</sup>

### **Monitoring until patient is stabilised**

UK guidance recommends that TSH monitoring should not occur within 6-8 weeks of a dosage change as this is the minimum period required to achieve stable concentrations.<sup>1,2,7</sup> However earlier consensus guidance recommends that TSH should be checked after 3-4 wks in the elderly, esp. if IHD present.<sup>5</sup>

### **Ongoing monitoring**

Once TSH levels and dosage of levothyroxine are stable check TSH level again after 4-6 months and then annually.<sup>1,2,7</sup>  
NICE support annual monitoring of TSH as a means of monitoring adherence and ensuring the dose of levothyroxine is still correct<sup>8</sup>

### **Action required if abnormal results**

The dose of levothyroxine should be individualized on the basis of clinical and biochemical (thyroid function tests) response with the aim of restoring physical and psychological well-being which maintaining normal lab range TSH levels and avoiding overtreatment. Doses of levothyroxine should be adjusted in increments of 25-50 micrograms every 3-4 weeks according to response. For people aged over 50 years and people with cardiac disease or severe hypothyroidism: doses should be adjusted in increments of 25 micrograms every 4 weeks according to response.<sup>1,2,7</sup>

### **Additional notes**

Pre-treatment ECG is considered valuable as changes induced by hypothyroidism may be confused with evidence of ischaemia.<sup>1,3</sup>  
A change in requirement for thyroid hormone can occur with ageing.<sup>2</sup>

The MHRA have acknowledged that patients with thyroid cancer, heart disease and pregnancy may be more sensitive to levels of thyroid hormone and require careful dosage titration over the long-term. However no further recommendations have been made on the monitoring of these patients.<sup>6</sup>

Caution is recommended when prescribing thyroxine to patients with adrenal insufficiency, age > 50 years, cardiovascular disorders.<sup>1,3</sup>

## References

1. CKS. Hypothyroidism. Last revised in April 2016.
2. UK Guidelines for thyroid function tests by Assoc. Clinical Biochemistry, British Thyroid Assoc and British Thyroid Foundation (Jun 2006)
3. SPC for levothyroxine sodium (Eltroxin 100mcg; Concordia International). Last revised Feb 2016
4. BNF accessed via Medicines Complete (last updated Apr 2017)
5. Consensus statement for good practice and audit measures in management of hypothyroidism & hyperthyroidism BMJ 1996; 313:539-544
6. MHRA. Levothyroxine Drug Products: A Review of Clinical & Quality Considerations (Jan 2013). Available at:
7. Management of primary thyroidism: statement by the British Thyroid Association Executive Committee. Clin Endocrinology 2015: 1-10
8. NICE: Indicator NM99 (hypothyroidism) for the NICE menu for the QOF. Published Aug 2015.

## Valproate and sodium valproate

### Tests prior to starting treatment

Valproate should only be initiated in adults and children by, or on the recommendation of, a specialist.<sup>4,6</sup>

**In January 2015, the MHRA issued a strengthened warning stating that valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated<sup>4,8,9</sup>.**

In 2017 NHS Improvement reinforced this message and issued a Patient Safety Alert to ensure that prescribers have systems in place to utilise signposted resources to support fully informed decisions on the use of valproate by girls and women of childbearing age<sup>8</sup>

Risk management materials for sodium valproate (Epilim) and valproate semisodium (Depakote) are also available on the eMC website (access via the relevant SPC)

LFTs, FBC (including platelet count, bleeding time and coagulation tests) and BMI/weight<sup>1,2,5,6</sup>

Make sure there is no undue potential for bleeding<sup>5</sup>

If used for bipolar disorder NICE additionally recommend assessment of <sup>6</sup>:

- diet, nutritional status and level of physical activity.
- cardiovascular status, including pulse and blood pressure
- metabolic status, including fasting blood glucose, glycosylated haemoglobin (HbA1c) and blood lipid profile

### Monitoring until patient is stabilised

LFTs periodically within first 6months of treatment especially in patients most at risk <sup>5</sup>.

**Commented [d48]:** Periodically may need to be clarified locally or on a patient-by-patient basis.

### Ongoing monitoring

FBC (including platelet count), bleeding time and coagulation tests are recommended before surgery<sup>4,5</sup>, and in cases of spontaneous bruising or bleeding<sup>1</sup>

LFTs, FBC and BMI after 6 months <sup>2,5,6</sup> and then annually<sup>6</sup>

Regular blood level test monitoring is not recommended as routine, and should be done only if clinically indicated (eg evidence of ineffectiveness, poor adherence, toxicity or clotting studies before surgery).<sup>4,6</sup>

A structured routine review of all people with epilepsy in primary care is recommended at least annually to assess: seizure control and adverse effects of treatment.<sup>7</sup>

**Commented [d49]:** There is also a view that blood level test monitoring may be helpful in guiding practice when used in pregnancy – see additional notes

As part of annual physical monitoring for patients with bipolar disorder NICE additionally recommend: CV status (incl pulse and BP), metabolic status (incl fasting blood glucose, HbA<sub>1c</sub>, and blood lipid profile<sup>6</sup>.

### Action required if abnormal results

Raised liver enzymes are usually transient but patients should be assessed clinically and FBC (including platelets) and liver function (including prothrombin time and coagulation tests) monitored until return to normal. Discontinue if abnormally prolonged prothrombin time, abnormal liver function or blood dyscrasias<sup>1,5,6</sup>

Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase). In case of pancreatitis, valproate should be discontinued.<sup>1,5</sup>

### Additional notes

Patients/carers should be told how to recognise signs of blood or liver disorders and advised to seek immediate medical attention if symptoms develop. Similarly they should be told how to recognise the signs of pancreatitis and advised to seek immediate medical attention if symptoms such as abdominal pain, nausea and vomiting develop.<sup>1,5,6</sup>

Valproate is classified as a category 2 drug (ie clinical judgement is required when switching between branded original and generic products for epilepsy only).<sup>3</sup>

Risk of abnormal pregnancy outcomes: a patient guide and card should be provided to all female patients<sup>5,8,9</sup>

Valproate should not be used during pregnancy and in women of childbearing potential unless clearly necessary ie with specialist neurological or psychiatric advice as appropriate depending on the indication. If required during pregnancy, the lowest effective dose is recommended divided over the day or controlled-release tablets to avoid rapid peaks in plasma level. Folate supplementation should be started before pregnancy as appropriate. Specialist prenatal monitoring should be instigated to detect possible occurrence of neural tube defects or other malformations when valproate has been used.<sup>1,3 5,6,8,9</sup>

Risk management materials for sodium valproate (Epilim) and valproate semisodium (Depakote) are available on the eMC website (access via the relevant SPC)

### References

1. Summary of Product Characteristics for Epilim. Date of revision of the text Nov 2016
2. The South London and Maudsley NHS Trust, Oxleas NHS trust 2012 Prescribing Guidelines 11th edition.
3. Drug Safety Update volume 7 issue 4, November 2013: A2.
4. NICE Clinical Guideline 137: The epilepsies: diagnosis and management of the epilepsies in adults in primary and secondary care (January 2012; last modified: Feb 2016)
5. BNF : accessed via Medicines Complete (Apr 17)
6. NICE Clinical Guideline 38: The management of bipolar disorder in adults, children and adolescents in primary and secondary care (Sept 2014, last updated Sep 2016)
7. Clinical Knowledge Service: Epilepsy (June 2015)

8. NHS Improvement and MHRA. Supporting the safety of girls and women being treated with valproate. (April 2017). Available via: <https://improvement.nhs.uk/news-alerts/supporting-safety-girls-women-treated-valproate/>
9. MHRA: Valproate and risk of abnormal pregnancy outcomes: new communication materials. Feb 2016. Available via: <https://www.gov.uk/drug-safety-update/valproate-and-of-risk-of-abnormal-pregnancy-outcomes-new-communication-materials>

## Warfarin

### Tests prior to starting treatment

FBC (incl platelets)<sup>1</sup>

Coagulation screen<sup>1</sup>

Renal function<sup>1</sup>

Liver function<sup>1</sup>

Thyroid status<sup>4</sup>.

BP<sup>5</sup>

(local practice may vary to also include FBC, U+E's and blood group and antibodies (aka Group and Save).

**Commented [d50]:** Needed in conjunction with renal function and liver function if want to calculate HAS-BLED score

### Monitoring until patient is stabilised

For rapid anticoagulation, SIGN guidelines recommend daily INR for a minimum of 4 days until desired INR is achieved by adjusting dose according to result and age<sup>1</sup>. Between days 5-14 the INR should be tested every 2-3 days until stable. They note that more careful dosing and monitoring may be required in elderly patients or where there is coadministration with drugs known to increase or decrease INR.

More generally CKS recommend that if rapid anticoagulation is required warfarin should be initiated at a dose of 5 mg or 10 mg once a day for 2 days and re-measure the person's international normalized ratio (INR) on day three<sup>5</sup>. However for people with atrial fibrillation there is no need to achieve anticoagulation rapidly; a slow-loading regimen is safe and achieves therapeutic anticoagulation in the majority of people within 3–4 weeks.

### Generally, CKS<sup>5</sup> recommend that the INR should be measured:

- **Daily, or on alternate days**, until it is within the therapeutic range (usually between 2.0 and 3.0, ideally 2.5) on two consecutive occasions.
  - Note: although the INR may be measured each day after starting warfarin, a meaningful INR can only be obtained 3–4 days after starting treatment.
- **Then, twice weekly** for 1–2 weeks, followed by weekly measurements until at least two INR measurements are within the therapeutic range.
- **Thereafter**, depending on the stability of the INR, at longer intervals (for example, up to every 12 weeks, if agreed locally). Once a stable warfarin dose that controls the INR has been established, changes in dose are seldom required.

### Ongoing monitoring

12 weekly monitoring of INR is considered acceptable in patients stabilised on warfarin<sup>2,5</sup>

- More frequent routine monitoring (e.g. every 1-2 weeks) of the INR is recommended if the person has an increased risk of overcoagulation: people with severe hypertension, liver disease (including alcoholic liver disease) or renal failure.
- Is at increased risk of bleeding: people on high intensity anticoagulation (INR more than 4.0); age 65 years or over; highly variable INRs; history of gastrointestinal bleeding; uncontrolled hypertension; cerebrovascular disease; serious heart disease; risk of falling; thrombocytopenia, anaemia, or coagulation disorders; malignancy;

trauma, renal insufficiency; morbidity changes (such as intercurrent illness, or exacerbations of chronic conditions); or has changed their medication (for example, when starting or stopping prescribed or over-the-counter medicines).

- May find adherence difficult.<sup>4</sup>

If an interacting drug is given for more than 7 days, check INR 3 to 7 days after start of this drug and adjust warfarin dose on the basis of the INR.<sup>3</sup>

Those who have had a change in warfarin dose as a result of an interacting drug will need to resume usual maintenance dose following cessation of that drug.<sup>2</sup>

### **Action required if abnormal results**

People with hypothyroidism or hyperthyroidism should be closely monitored on starting warfarin therapy<sup>4</sup>. Similarly if the person or another family member is known to have polymorphisms of CYP2C9 or VKORC1, extra care is warranted.

If the patient's HASBLED score is more than 3, then the patient is at a high risk of bleeding and warfarin should be used cautiously, with regular reviews.<sup>5</sup>

Establish reason for abnormal INR reading (e.g. missed doses/ inadvertent change in dose, interacting drug, change alcohol intake, significant change in diet, intercurrent illnesses)

Low reading: refer to local anticoagulation guidelines for use of booster doses and how to increase maintenance dose if needed.

High reading: risk of bleeding increases greatly once INR > 5

Refer to local anticoagulant guidelines for advice on number of days to stop therapy and adjustment of maintenance dose if needed further action may also be needed depending on whether there is minor or major bleeding.<sup>2</sup>

For INR > 8, oral anticoagulants should be stopped and advice sought from haematologist on management.<sup>2</sup>

Patient characteristics such as older age, uncontrolled hypertension, diabetes, renal or liver failure, previous gastrointestinal or cerebral bleed and use of anti-platelet medication are associated with a higher risk of bleeding.<sup>2</sup>

### **Additional notes**

Refer to BNF when prescribing any new drug to patient taking warfarin.

Prescribers should ensure that they are compliant with NPSA recommendations on actions that can make anticoagulant therapy safer.<sup>4</sup>

Ensure patient is given an anticoagulant treatment booklet; this is often referred to as the 'Yellow book'. It includes advice for people taking anticoagulants (e.g. adverse effects), an alert card, and a section for recording the international normalized ratio (INR) results.<sup>5</sup>

Patients should be advised to always carry their anticoagulant alert card with them at all times, and they should always take their anticoagulant treatment booklet when they go to the warfarin clinic to have their INR checked.<sup>5</sup>

The MHRA has recently issued a warning that warfarin may be associated with calciphylaxis. Patients should be advised to consult their doctor if they develop a painful skin rash.<sup>7</sup>

## References

1. SIGN Guideline 129 • Antithrombotics: indications and management (last updated June 2013). Available: <http://www.sign.ac.uk/assets/sign129.pdf>
2. British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin – third edition. Br J Haematol 1998; 101: 374–387
3. British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin – fourth edition. Br J Haematol 2011; 154: 311–324
4. NPSA Actions that can make anticoagulant therapy safer (Mar 2007)
5. CKS. Oral anticoagulation – updated May 2013
6. HAS-BLED score for bleeding risk on oral anticoagulation in atrial fibrillation (AF). Accessed via: <http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20110126115649933383> on 25/02/2014
7. Warfarin: reports of calciphylaxis. MHRA (2016). Available: <https://www.gov.uk/drug-safety-update/warfarin-reports-of-calciphylaxis>