

Suggestions for Drug Monitoring in Adults in Primary Care

February 2014

A collaboration between London and South East Medicine 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 reviewed and update this document again in 2016 , to check if this is the latest edition visit the NICE Evidence Services website at www.evidence.nhs.uk alternatively contact David Erskine at London and South East Regional Medicines Information, email david.erskine@gstt.nhs.uk

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A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

ACE inhibitors and angiotensin II receptor antagonists

Tests prior to starting treatment

U&Es (incl urea and creatinine)^{1,3} and eGFR¹

In patients with CKD measure serum potassium and estimate GFR before starting ACEI/ARB therapy²

BP^{1,3,6}

See BNF for more detail regarding initiation in patients with hyponatraemia, hypovolaemia, severe or unstable heart failure, known renovascular disease, hypotensive or taking multiple or high-dose diuretics or high-dose vasodilators.⁴

Seek further advice if patient with hypertension has serum creatinine >200 micromol/L or eGFR < 30ml/min, or confirmed renovascular disease before initiating treatment⁵

In patients with CKD, ACEI/ARB therapy should not normally be started if the pre-treatment serum potassium is significantly above normal reference range (typically >5.0mmol/L)^{1,2}

Monitoring until patient is stabilised

HEART FAILURE

Measure serum urea, creatinine and electrolytes 1-2 weeks after initiation and after each dose increment.¹ In Best Practice series it is advised that these tests are conducted after 5-7 days in higher-risk patients (e.g. those receiving spironolactone, those with existing renal dysfunction, and those receiving combination therapy)⁵
Monitor BP.¹

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.³

In Best Practice series it is advised that renal function should be checked one week after starting treatment or changing dose in patients with hypertension. If patient is judged to be at higher risk of developing hyperkalaemia or deteriorating renal function (e.g. peripheral vascular disease, diabetes, pre-existing renal impairment or an older patient) renal function should be checked within 4-10 days⁵

CKD

Measure serum urea, creatinine and electrolytes 1-2 weeks after initiation and after each dose increment.²

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Post-MI

Measure renal function (serum creatinine), electrolytes and BP 1-2 weeks after initiation and after each dose increment³

Ongoing Monitoring

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.¹

Monitor BP routinely¹

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 at least annually in stable hypertensive patients that do not have diabetes.⁶

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).⁷

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.³

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.^{1,2}

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.^{1,2}

If Na <132mmol/L specialist advice should be obtained⁵

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Significant drug interactions

- Ciclosporin
- Potassium-sparing diuretics and aldosterone antagonists
- Gold (sodium aurothiomalate) (applies to ACEIs only)
- Lithium
- Potassium salts

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 (2008)
3. NICE Clinical Guideline 172 – Secondary prevention for patients in primary and secondary care following a myocardial infarction (2014)
4. BNF Issue 66
5. Best Practice in primary care pathology: review J Clin Pathol 2007;60:225-234
6. CKS Guideline on hypertension (not diabetic) (2012)
7. CKS Guideline on chronic kidney disease (not diabetic) (2009)

Acetylcholinesterase inhibitors – donepezil, galantamine, rivastigmine

Tests prior to starting treatment

Renal function (if galantamine or rivastigmine)¹
Liver function¹

Monitoring until patient is stabilised

None

Ongoing Monitoring

None identified

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)

Additional notes

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 function².

Specialist initiation only but may be continued and monitored by the GP under a shared care protocol.^{1,2}

Significant drug interactions

None noted

References

1. BNF 66. September 2013
2. Clinical Knowledge Summary. Dementia. Last revised March 2010

Amiodarone

Tests prior to starting treatment

Treatment should normally be initiated and monitored under hospital or specialist supervision¹

Thyroid stimulating hormone (TSH)¹⁻⁴

Free T4 and T3 measured if TSH is abnormal³⁻⁵

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



LFTs (particularly transaminases)^{1,4,5}

U&Es^{4,5}

ECG and potassium level^{1,4,5}

Chest X-ray^{1,2,4,5}

Monitoring until patient is stabilised

In warfarinised patients, more frequent monitoring of INR both during and after amiodarone treatment is recommended¹; initially weekly for first 7 weeks⁵

Ongoing monitoring

TSH every 6 months¹⁻⁵ and for some months after discontinuation¹ (UK guideline on TFTs suggests up to 12 months after cessation³)

Serum TSH should also be measured when thyroid dysfunction is suspected.¹

LFTs every 6 months^{1,4,5}

U&Es every 6 months^{4,5}

Chest X-ray every 12 months^{4,5}

ECG every 12 months^{4,5}

Unless blurred or decreased vision occurs, ophthalmological examination is recommended annually¹, although the DTB states that these are usually only necessary for patients with visual symptoms⁶

Action required if abnormal results

If TFTs are borderline repeat test in 6 weeks⁷

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.¹

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Amiodarone-associated hyperthyroidism should be diagnosed only if high circulating free T4 is associated with high or high/normal free T3 and undetectable TSH³; such a diagnosis should prompt withdrawal of amiodarone¹ and specialist referral.³ 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.¹

Diagnosis of hypothyroidism 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.¹

Treatment should be discontinued if severe liver function abnormalities or clinical signs of liver disease develop²

If blurred or decreased vision occurs, complete ophthalmologic examination including fundoscopy should be promptly performed.¹

Appearance of optic neuropathy and/or optic neuritis requires amiodarone withdrawal due to the potential progression to blindness¹ and expert opinion sought²

If pulmonary toxicity is suspected, chest X ray should be repeated and lung function tested, including where possible, measurement of transfer factor.¹ Specialist referral advised.⁶ Pneumonitis should always be suspected if new or progressive shortness of breath or cough develops in a patient taking amiodarone²

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.²

Fresh neurological symptoms should always raise the issue of peripheral neuropathy²

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 light²

Because of long half-life of amiodarone, clinical problems may occur up to a year after stopping the drug³ (hyperthyroidism may occur up to several months after discontinuation¹).

Few if any laboratories routinely measure free T4 and free T3 in standard thyroid profiles; many use a TSH measurement to screen for primary thyroid disease before performing further tests.⁴

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.⁴

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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 disorders³

Significant drug interactions

Note: Amiodarone has a long half life and the full effects of drug interactions may thus take several weeks to develop on starting interacting drug and to wane on stopping it.⁶ Only specialists should co-prescribe and monitor drug therapy that prolongs the QT interval.⁶

- Anti-arrhythmics (disopyramide, flecainide, dronedarone)
- Antibacterials (erythromycin, levofloxacin, moxifloxacin, telithromycin)
- Anticoagulants (coumarins, phenindione, dabigatran)
- Antimalarials (chloroquine, hydroxychloroquine, mefloquine, quinine, artemether with lumefantrine, piperazine with artemimol)
- Antipsychotics (which prolong QT interval: amisulpride, benperidol, droperidol, phenothiazines, haloperidol, pimozide, sulpiride, zuclopenthixol).
- Antivirals (atazanavir, fosamprenavir, indinavir, saquinavir, ritonavir, telaprevir)
- Arsenic trioxide
- Atomoxetine
- Beta-blockers (all including sotalol)
- Bosutinib
- Calcium channel blockers (diltiazem and verapamil)
- Colchicine
- Cobicistat
- Digoxin
- Fingolimod
- Ivabradine
- Lithium
- Mizolastine
- Simvastatin (avoid doses >20mg/d)
- Pentamidine
- Phenytoin
- Tolterodine
- Tricyclic antidepressants
- Vandetanib

References

1. Summary of Product Characteristics for Cordarone 100mg and 200mg Tablets. SPC (date of revision April 2011)
2. BNF Issue 66 (Sept 2013)
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
4. Smellie, WSA, Coleman JJ. Pitfalls of testing and summary of guidance on safety monitoring with amiodarone and digoxin. BMJ 2007;334:312-5
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/>

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

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>

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Antipsychotic agents

Tests prior to starting treatment

FPG^{2, 4,5,,6}

HbA1c²

BP^{1,3,4,5,6}

Pulse²

FBC^{3,4,5}

LFTs^{1,3, 4,5}

U&Es^{1,3,4,5}

Fasting lipids^{1,2,3,4,6}

CPK^{1, 4}

Smoking history⁶

Weight (include waist circumference)^{1,2,3,4,5,6}

BMI^{1,3,4,5,6}

Height³

TSH³

Prolactin^{1,2,3,4} - CKS states that this is not required for olanzapine (<20 mg daily)⁵ and SIGN recommends only if clinically indicated.⁶

ECG^{1,2,4} - NICE/SIGN recommends if clinically indicated or recommended in SPC for that product.^{2,3,6} CKS states not required for conventional doses or absence of other predisposing factors, such as relevant personal or family history, co-prescription of QT-prolonging drugs, or electrolyte imbalance)⁵.

Monitoring until patient is stabilised

BP: in schizophrenia NICE recommend monitoring at 12 weeks.²

Other guidelines recommend frequent checks during dose titration phase^{1,4,5} or at 1 month (if clinically indicated) and 3 months.⁶

Pulse: NICE recommend monitoring at 12 weeks.²

FPG: In schizophrenia NICE recommend monitoring at 12 weeks². Other guidelines recommend checking after 1 month then every 4-6 months⁵ or at 1 month (if clinically indicated) and 3 months^{3, 6} (and more often if elevated)³.

HbA1c: In schizophrenia NICE recommend monitoring after 12 weeks.²

Weight: In schizophrenia NICE recommend weekly for first 6 weeks and then at 12 weeks and 1 year plotted on a chart.²

Other guidelines recommend every 3 months for 1st year^{1,4,5}, or at 1 month (if clinically indicated) and 3 months⁶

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Lipids: In schizophrenia NICE recommend assessment at 12 weeks². Other guidelines recommend every 3 months for first year^{1,3,4,5}, or at 1 month (if clinically indicated) and 3 months⁶ (or more often if weight gain is rapid)³.

ECG: After each dose change^{1,5} or if clinically indicated⁶

Prolactin: At 6 months^{1,4,5} or if clinically indicated⁶

Smoking history at 3 months⁶

Ongoing monitoring

Every 12 months: FBC, U&Es, LFTs, weight, lipids, prolactin, BP, FPG.^{1,4,5,6} NICE also recommend measurement of waist circumference, pulse, and HbA1c every 12 months in patients being treated for schizophrenia²

Other guideline producers recommend FPG measurements every 4-6 months.^{1,4,5} 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.²

CPK if neuroleptic malignant syndrome (NMS) suspected¹

TFTs (every 6 months if rapid-cycling but otherwise every 12 months).³

Smoking history⁶

Action required if abnormal results

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

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

If ECG abnormal, refer to cardiologist.¹

If hyperprolactinaemia confirmed and symptomatic, switch drugs.¹

If NMS suspected, stop therapy¹

If LFTs indicate hepatitis (transaminases x3 normal) or functional damage (PT or albumin change), stop therapy¹

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.²

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NICE recommend a regular and systematic assessment of overall physical health and adherence whilst on treatment.²

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.⁴

Patients with schizophrenia should have physical health monitoring (including cardiovascular disease assessment) at least once per year.^{4,6}

Dose adjustment may be necessary if smoking started or stopped during treatment.⁴

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

Significant drug interactions

- Anaesthetics (general)
- Analgesics (methadone)
- Anti-arrhythmics
- Antibacterials (see BNF for detail)
- Antidepressants (see BNF for detail)
- Antiepileptics
- Antifungals
- Antimalarials
- Antivirals
- Anxiolytics and hypnotics
- Aprepitant (pimozide)
- Atomoxetine
- Beta-blockers
- Cytotoxics
- Diuretics
- Grapefruit juice (quetiapine)
- Hormone antagonists (specific to tamoxifen with droperidol)
- Ivabradine (pimozide)
- Penicillamine (clozapine)
- Pentamidine
- Tacrolimus (droperidol)


References

1. The South London and Maudsley NHS Trust, Oxleas NHS Trust 2012 Prescribing Guidelines 11th 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 (Jul 2006)
4. BNF March-September 2013; Issue 65
5. Clinical Knowledge Summaries: Schizophrenia. Last revised October 2009
6. SIGN 131: Management of schizophrenia. March 2013

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Apixaban

Tests prior to starting treatment

Renal function^{1-3, 7}
Body weight¹⁻²
Baseline clotting screen^{3,7}
Full blood count^{3,7}
LFTs^{2-3,6}
BP⁴ 

Monitoring until patient is stabilised

No routine anticoagulation monitoring is needed¹⁻³

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 medicines⁶

Ongoing monitoring

No routine anticoagulation monitoring is needed¹⁻³

Patient compliance should be assessed every three months ideally^{3,7}

Enquire about presence of any adverse effects, in particular signs and symptoms of bleeding and anaemia, every three months ideally^{1-3,7}

Renal function may decline whilst on treatment so it should be monitored annually for patients with CrCl > 60ml/min or every six months for patients with CrCl 30-60ml/min or every three months if the person has a CrCl between 15-30ml/min^{3,7}

LFTs annually^{3,7}

Full blood count annually^{3,7}

Action required if abnormal results

If CrCl < 15ml/min stop apixaban, assess for bleeding and seek advice regarding alternative anticoagulation therapy.

Reduce the dose to 2.5mg twice daily if the person's eGFR is 15-29ml/minute/1.73m², or if serum creatinine is 133micromol/L and the patient is aged 80 years or older or weighs less than 60kg⁷

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

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.⁴

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

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Additional notes

Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. It should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. It should be restarted after the procedure/surgery as soon as possible provided adequate haemostasis has been established.²

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

Significant drug interactions

- Analgesics (intravenous diclofenac, ketorolac)
- Anticoagulants
- Antifungals (e.g. ketoconazole, itraconazole, posaconazole and voriconazole)

References

1. British National Formulary. Accessed online via: www.bnf.org on accessed on 29/11/13
2. Eliquis. Summary of Product characteristics for apixaban 2.5mg tablets. Last updated on the eMC 19/09/2013 Accessed via: www.emc.medicines.org.uk on 25/02/2014
3. Heidbuchel, H., Verhamme, P., Alings, M. et al, **2013**. European Heart Rhythm Association practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 15, 625-651
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 25/02/2014
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7. 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/pl-p/documents/drugsafetymessage/con321961.pdf>
8. CKS – Anticoagulation-oral (last revised May 2013)


Azathioprine

Tests prior to starting treatment

FBC (with differential white cell count)⁴

LFTs¹

U&Es incl creatinine¹

TPMT assay¹ 

Consider NICE recommendations regarding screening for hepatitis B and C in patients at increased risk of infection⁶

Baseline HIV status should also be established in those with risk factors⁴.

Monitoring until patient is stabilised

IN RHEUMATOLOGY

FBC and LFTs weekly for 6 weeks and continue every 2 weeks until dose stable for 6 weeks, then monthly thereafter¹.

Following a change in dose repeat FBC and LFTs after 2 weeks and then monthly¹

IN DERMATOLOGY

FBC and LFTs weekly until stable on maintenance dose. Otherwise same as for rheumatology.¹

IN GASTROENTEROLGY

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 practice³

IN GENERAL

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

Ongoing monitoring

IN RHEUMATOLOGY

Once the maintenance dose has been achieved and stable for 6 months consider discussing with patient to reduce monitoring of FBC and LFTs to 3-monthly unless the patient is heterozygote for TPMT in which case monitoring should continue at monthly intervals at a minimum.¹

U&Es and creatinine should be monitored every 6 months¹

IN DERMATOLOGY

Same as for rheumatology¹

IN GASTROENTEROLGY

BSG suggest monitoring FBC every 4 to 8 weeks³

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IN GENERAL

BNF recommends a minimum of 3-monthly FBC monitoring²



Action required if abnormal results

Withhold treatment until discussion with consultant specialist if¹:

- WBC < 3.5 x 10⁹/l,
- Neutrophils < 2 x 10⁹/l
- Platelets < 150 x 10⁹/l,
AST, ALT increase to > twice the upper limit of normal
- Rash or oral ulceration occurs.¹
- abnormal bruising or severe sore throat occurs (withhold until FBC available)

If MCV > 105fl: check B12, serum folate and TSH – withhold until results are available and discuss with specialist¹

Additional notes

Pneumococcal vaccine and annual flu vaccine should be given, but live vaccines should be avoided⁴.

In patients exposed to chickenpox or shingles, passive immunisation should be carried out using VZIG¹.

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 jaundice⁴.

Sunscreens and protective clothing should be encouraged to reduce sunlight exposure¹

Significant drug interactions

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 jaundice⁴.

Sunscreens and protective clothing should be encouraged to reduce sunlight exposure¹

- | | |
|--|---|
| • Allopurinol: BSR and BHPR recommend the reduce azathioprine dose to 25% of the original ¹ : | • Warfarin – may need to reduce dose of azathioprine or increase dose of warfarin (consult specialist) |
| • Antibacterials (co-trimoxazole and trimethoprim) | • Phenytoin, Sod. Valproate, Carbamazepine – azathioprine reduces the absorption of these |
| • Anticoagulants (coumarins) | • ACEIs: co-prescription of azathioprine may cause anaemia - if significant consider alternative to ACE inhibitor or different DMARD. |
| • Antivirals (ribavirin) | |
| • Febuxostat | |

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BAD advise more cautious dosing and increased monitoring of FBC if co-prescribed with aminosalicylates as they inhibit TMPT in vitro (but clinical significance is unclear)⁴.

The risk of haematological adverse reactions is increased when azathioprine is used with any drug that has a potential myelotoxic effect. Caution must be exercised with co-prescription of azathioprine and any of these drugs, and more frequent monitoring of FBC is advised⁴.

References

1. BSR and BHPR guideline for disease-modifying anti-rheumatic drug therapy (DMARD) in consultation with the British Association of Dermatologists. (2008)
2. BNF Issue 65 (March-September 2013)
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) 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

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Carbimazole

Tests prior to starting treatment

TFTs: All patients with hyperthyroidism should be referred to a specialist at diagnosis to establish the diagnosis and optimal management plan^{1,2}
WBC³

Monitoring until patient is stabilised

UK Guidelines recommended TFTs every 4-6 weeks after initiation. The frequency should be reduced to approximately every 3 months once a maintenance dose is achieved².

Ongoing monitoring

UK Guidelines recommend annual monitoring once stable if being used as a long-term treatment option.²

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

Action required if abnormal results

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 neutropenia⁴
Repeat WBC if patient develops fever, mouth ulcers, sore throat or other symptoms of infection⁴
Stop drug and recommend immediate specialist referral if leucocyte count falls to $<1500 \times 10^6/L$ or neutrophil count to $<500 \times 10^6/L$ ³

Additional notes

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

Significant drug interactions

None listed

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

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. March-September 2013; Issue 65
5. SPC for carbimazole 20 mg tablets (Amdipharm Mercury Company Limited). Last revised May 2013

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

Ciclosporin (Neoral)

Tests prior to starting treatment

Rheumatology and dermatology

FBC (incl. differential white cell count), U&Es (particularly noting creatinine; x2 two weeks apart to obtain mean value), LFTs, fasting lipids.

BP should be $\leq 140/90$ on 2 separate occasions two weeks apart prior to treatment or treat hypertension prior to treatment¹

In psoriatic arthritis consult a dermatologist if patient has received in excess of 1000J PUVA before initiating treatment¹

For atopic dermatitis and psoriasis, the BNF advises dermatological and physical examination (inc BP and renal function) at least twice before starting treatment².

In gastroenterology

BSG recommend that blood cholesterol and magnesium be checked before starting therapy, and that BP, FBC and renal function be checked at baseline⁴

In general

BNF recommends measurement of blood lipids before treatment².

Consider NICE recommendations regarding screening for hepatitis B and C in patients at increased risk of infection⁶

Monitoring until patient is stabilised

In general

In addition to the various parameters discussed below, the BNF also recommends measuring blood lipids after the first month of treatment and monitoring serum magnesium (no frequency stated)²

Rheumatology and dermatology

FBC and LFT monthly until dose and trend stable for 3 months (if applicable).¹

Serum electrolytes (including K and creatinine) every two weeks until dose and trend stable for 3 months (if applicable).¹

Check BP each time patient attends clinic and maintain $\leq 140/90$ ¹

Check fasting lipids periodically¹

For patients with rheumatoid arthritis, atopic dermatitis and psoriasis, the BNF recommends creatinine every 2 weeks for first 3 months²

In gastroenterology

BP, FBC, renal function and ciclosporin level (aim for 100-200ng/ml) at weeks 1 and 2 then monthly⁴


A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

In transplantation

No specific guidance identified

Ongoing Monitoring

In general

In addition to the various parameters covered below, the BNF also recommends monitoring serum magnesium (no frequency stated)² 

Rheumatology and dermatology

FBC and LFT every 3 months¹

Serum electrolytes (including K and creatinine) every month (take extra care if NSAID added, particularly diclofenac)¹

Check BP each time patient attends clinic and maintain $\leq 140/90$.¹


Check fasting lipids periodically¹

The BNF recommends creatinine every month for atopic dermatitis and psoriasis, and every month (for months 4-6) then every 4-8 weeks for rheumatoid arthritis (more frequently if dose increased or concomitant NSAIDs introduced or increased)².

In gastroenterology

BP, FBC, renal function and ciclosporin level (aim for 100-200ng/ml) monthly⁴

In transplantation

No specific guidance identified 

Action required if abnormal results

Withhold and talk to specialist if ¹ -

- Hypertension develops that cannot be controlled to $<140/90$ by anti-hypertensive drugs
- Creatinine rises by $>30\%$ of baseline on 2 consecutive occasions one week apart,
- Abnormal bruising (check FBC)
- Potassium rises above reference range
- Significant rise in fasting lipids
- Platelets $< 150 \times 10^9/L$
- >2 -fold increase in AST, ALT or ALP above upper limit of normal range

CKS notes that whilst absolute values are useful indicators, trends are equally important, and any rapid fall or consistent downward trend in any parameter warrants extra vigilance³.

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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)⁴

Additional notes

Oral formulations contain around 12% vol. ethanol, with a 500mg dose equivalent to 500mg ethanol (15mL beer or 5mL wine)⁵

Avoid excessive exposure to UV light, including sunlight²

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)². Switching should be made with caution and under specialist supervision⁵.

Significant drug interactions

- ACE inhibitors
- Aliskiren
- Ambrisentan
- Analgesics (NSAIDs, diclofenac)
- Angiotensin-II receptor antagonists
- Antibacterials (clarithromycin, erythromycin, rifampicin, sulfadiazine, aminoglycosides, polymyxins, quinolones, sulfonamides, vancomycin, chloramphenicol, telithromycin, daptomycin, macrolides, trimethoprim)
- Anticoagulants (dabigatran)
- Antidepressants (St John's wort – BSR advise that it decreases ciclosporin activity¹)
- Antiepileptics (carbamazepine, phenobarbital, phenytoin)
- Antifungals (fluconazole, itraconazole, voriconazole, miconazole, posaconazole, caspofungin, amphotericin)
- Antimalarials (chloroquine, hydroxychloroquine)
- Antivirals (atazanavir, ritonavir, boceprevir, fosamprenavir, indinavir, efavirenz, saquinavir, telaprevir)
- Beta-blockers (carvedilol)
- Bile acids (ursodeoxycholic acid)
- Bosentan
- Calcium channel blockers (lercanidipine, diltiazem, nicardipine, verapamil, BSR advise that nifedipine should only be used with caution¹)
- Cardiac glycosides (digoxin – BSR advise that levels can be increased¹)
- Colchicine (BSR advise to avoid¹)
- Corticosteroids (methylprednisolone)
- Cytotoxics (melphalan, doxorubicin, epirubicin, everolimus, idarubicin, methotrexate, crizotinib)
- Diuretics (acetazolamide, potassium-sparing and aldosterone antagonists)
- Grapefruit juice
- Hormone antagonists (danazol, octreotide, pasireotide)
- Lenalidomide
- Lipid regulating drugs (colesevelam, atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin, ezetimibe; BSR advise use of simvastatin at a max dose of 10mg/day¹)
- Metoclopramide
- Modafinil
- Orlistat
- Potassium salts
- Sulfapyrazone
- Tacrolimus
- Ulcer-healing drugs (cimetidine)

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Patients receiving ciclosporin must not receive immunisation with live vaccines¹.

References

1. BSR and BHPR guideline for disease-modifying anti-rheumatic drug therapy (DMARD) in consultation with the British Association of Dermatologists. (2008)
 - a. BNF Issue 66
2. Clinical Knowledge Service Guidance – DMARDs (Jan 2013)
3. BSG Guidelines for the management of inflammatory bowel disease in adults – Gut 2011,
4. Summary of Product Characteristics for Neoral Soft Gelatin Capsules, Neoral Oral Solution. Date of revision of the text Feb 2012
5. NICE public health guidance 43: Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (2012)

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

Corticosteroids (long term oral therapy)

Tests prior to starting treatment

Blood pressure^{1,2}

Body weight^{1,2}

BMI²

Height (children and adolescents)^{1,2}

Ophthalmic examination (consider advising person to see optician for baseline assessment)¹

Fasting glucose level^{1,2}

Triglycerides^{1,2}

Potassium¹

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 osteoporosis²

DEXA scan for people aged <65years with no previous fragility fracture who are due to start a course likely to last ≥ 3 months. Consider starting treatment if there is a long wait for DEXA scanning.¹

Monitoring until patient is stabilised

Triglycerides and potassium — check 1 month after start of therapy¹

Check for new onset of diabetes 1 month after start of therapy¹

Ongoing monitoring

Blood pressure — monitor at every appointment¹

Triglycerides every 6–12 months¹

Potassium every 6–12 months¹

Check for new onset of diabetes every 3 months- if possible, dipstick test urine for glucose at each clinic visit.¹

Monitor people with confirmed diabetes more closely¹

Body weight — monitor regularly¹

Record height of children and adolescents regularly.¹

Perform a falls risk assessment, where appropriate, and advise those at increased risk of fractures.¹

Monitor for signs of adrenal suppression.¹ 

DEXA scan for people aged <65years with no previous fragility fracture who have been taking oral corticosteroids for ≥ 3 months if no baseline DEXA scan results available.¹

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Annual eye exam; 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)²

Action required if abnormal results

Offer weight management advice if necessary.¹

Treat elevated BP if necessary¹

In patients with existing diabetes, oral antidiabetic drugs may need to be increased, or insulin therapy started¹

Refer children and adolescents to a paediatrician if growth suppression is suspected.¹

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

Consider referral if fracture risk is high and/or BMD is decreasing²

Additional notes

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 infections²

Offer bisphosphonates to prevent osteoporosis in people who have been taking oral corticosteroids for > 3months, or who are likely to do so, and who are:³

- 65 years of age or more.³
- Less than 65 years of age with a previous fragility fracture.³
- Less than 65 years of age without a previous fragility fracture and a T-score of – 1.5 or less.³

If drug treatment is not indicated because the T-score is between 0 and –1.5, repeat the DEXA scan in 1 to 3 years if corticosteroid use continues.³

Refer premenopausal women and men who are found to have osteoporosis to a specialist for further investigation and management.³

Significant drug interactions

Generally does not apply to inhaled or topical preparations unless specified

- | | |
|---|--|
| • Aldeslakin | • Itraconazole (with budesonide- all routes) |
| • Amphotericin | • Ketoconazole(with budesonide- all routes) |
| • Carbamazepine | • Phenobarbital |
| • Ciclosporin (with high dose methylprednisolone) | • Phenytoin |
| • Coumarin anticoagulants | |

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- Rifamycins
- Rilpivirine (with multiple doses of dexamethasone)
- Ritonavir (with budesonide or fluticasone- all routes)
- Vaccines (with high dose corticosteroids)

References


1. NICE. Corticosteroids-oral: Monitoring. CKS (last revised Aug 2010) accessed via: <http://cks.nice.org.uk/corticosteroids-oral#!scenariorecommendation:7>
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. NICE. Corticosteroids – oral: Minimising osteoporosis risk (Last revised in August 2010) accessed via <http://cks.nice.org.uk/corticosteroids-oral#!scenariorecommendation:6>

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

Dabigatran

Tests prior to starting treatment

Clotting screen, U&E's, LFTs, FBC²

BP⁶ 

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 medicines²

Ongoing monitoring

- U&E's, LFTs, FBC at least once a year especially in elderly and patients with renal impairment. ^{1,2,4,5}
- Repeat U&E's every 6 months if CrCl 30–60 mL/min, patient > 75 years or fragile. ^{2,4}
- Repeat U&E's every 3 months if CrCl 15–30 mL/min.²
- More frequent U&E's/LFTs advised if intercurrent illness that may impact renal or hepatic function. ^{2,5}

Action required if abnormal results

If renal function has declined, review treatment, as dabigatran may need to be stopped or a lower dose may be required. ^{2,5}

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

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.⁶

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. ^{3,4}

There is no specific antidote to dabigatran and excessive anticoagulation may require interruption of treatment. ⁴

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Dabigatran will need to be stopped between 24 hours and 4 days prior to elective surgery depending on renal function and the risk of associated bleeding⁵

Significant drug interactions

- Analgesics – NSAIDs, diclofenac, ketorolac
- Anti-arrhythmics – amiodarone, dronedarone
- Antibacterials - rifampicin
- Anticoagulants – apixaban, rivaroxaban
- Antidepressants – SSRI or SSRI related antidepressants
- Antifungals – ketoconazole, itraconazole
- Calcium channel blockers – verapamil
- Ciclosporin
- Sulfinpyrazone
- Tacrolimus

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

Digoxin

Tests prior to starting treatment

Renal function¹
U&Es² (paying particular attention to potassium level)^{1,3}

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.¹

Samples for digoxin measurement should be taken at least 8-12 hours after the last dose¹

Ongoing monitoring

Routine monitoring of serum digoxin concentrations is not recommended.^{1,4}
The presence of toxic symptoms such as nausea, vomiting, visual disturbance (yellow-green discoloration), or severe dysrhythmias may prompt an urgent measurement.¹

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

Monitoring frequency varies considerably depending on a patient's medical and drug history.³

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.³

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 overdose.⁵

Hypokalaemia predisposes the patient to digoxin toxicity.⁵

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.

6

Low potassium levels require correction.⁵

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Significant drug interactions

- Acetazolamide
- Amiodarone
- Amphotericin
- Chloroquine
- Ciclosporin
- Colchicine
- Diltiazem
- Dronedarone
- Hydroxychloroquine
- Itraconazole
- Lercanidipine
- Loop diuretics
- Nicardipine
- Nifedipine
- Propafenone
- Quinine
- Spironolactone
- St John's Wort
- Thiazides and related diuretics,
- Ticagrelor
- Verapamil

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 10 March 2012)
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 66 (September 2013)
6. Aronson JK, Hardman M. ABC of monitoring drug therapy. Digoxin. *BMJ* 1992, 305: 1149-52

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

Dronedarone

Tests prior to starting treatment


LFTs¹
Serum creatinine¹
ECG¹
U&Es (potassium and magnesium)²

Monitoring until patient is stabilised

LFTs after 7 days¹
Serum creatinine after 7 days¹

Ongoing monitoring

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

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

ECG should be repeated every 6 months¹

Action required if abnormal results

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

Dronedarone should not be initiated in patients if eGFR is less than 30 mL/minute/1.73 m².³

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.⁴ Further increases should prompt consideration of treatment discontinuation.¹ 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 m².

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

Within the SPC it is advised that if QTc Bazett interval is ≥500 milliseconds, dronedarone should be stopped.⁴

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

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

Additional notes

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.³ 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.³ Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity and patients should be carefully evaluated clinically.⁴

Significant drug interactions

- Amiodarone
- Disopyramide
- Clarithromycin
- Erythromycin
- Rifampicin
- Telithromycin
- Coumarins
- Phenindione
- Dabigatran
- St John's wort
- Tricyclic antidepressants
- Carbamazepine
- Phenobarbitone
- Phenytoin
- Ketoconazole
- Itraconazole
- Posaconazole
- Voriconazole
- Antipsychotics (that prolong QT interval)
- Phenothiazines
- Ritonavir
- Saquinavir
- Beta-blockers
- Sotalol
- Nifedipine
- Diltiazem
- Verapamil
- Digoxin
- Fingolimod
- Grapefruit juice
- Simvastatin

References

1. MHRA Drug Safety Update Oct 2011, vol 5 issue 3: A1. Accessed via <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON131928> (last accessed 21/9/13)
2. Dronedaron 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> (last accessed 21/9/13)
3. BNF No 65 – March – September 2013
4. Sanofi-Aventis. Summary of Product Characteristics for Multaq (Dronedaron). Last updated Aug 2013. Accessed via <http://www.medicines.org.uk/emc/medicine/22894/SPC/> (last accessed 21/9/13)

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

Eplerenone

Tests prior to starting treatment

U&Es (including creatinine) and eGFR^{1,3}

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.^{1,2,3,4}

Ongoing monitoring

U&Es (including Creatinine) and eGFR at 6 months and every 3 to 6 months thereafter.^{2,3,4} 

Action required if abnormal results

Eplerenone should not be started in patients with a baseline serum potassium greater than 5.0mmol/L, an eGFR of less than 30mL/minute or severely impaired liver function (Childs-Pugh Class C).¹

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 specialist⁴.

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.⁴

Additional notes

Advise patients to avoid NSAIDs not prescribed by a physician and salt substitutes high in potassium²

Significant drug interactions

- ACE inhibitors and Angiotensin-II receptor antagonists
- Alpha-blockers
- Antibacterials (clarithromycin, telithromycin, rifampicin)
- Antidepressants (St John's Wort)
- Antiepileptics (carbamazepine, phenytoin, phenobarbital)
- Antifungals (itraconazole, ketoconazole)
- Antivirals (nelfinavir, ritonavir)
- Ciclosporin
- Lithium
- Potassium salts
- Tacrolimus

Note, although not listed as a potentially hazardous interaction in the BNF eplerenone is contraindicated in patients receiving other potassium sparing diuretics¹

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

References

1. Summary of Product Characteristics for Inspra® 25mg & 50mg film-coated tablets (eplerenone). Date of revision of the text March 2012
2. SIGN Guideline No 95. Management of chronic heart failure. February 2007.
3. NICE Guideline No 48. MI: Secondary Prevention. May 2007.
4. NICE Guideline No 108. Chronic Heart Failure. Full Version. August 2010.

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

Hydroxycarbamide

Tests prior to starting treatment


FBC, U&Es, uric acid, LFTs^{1,2}

Consider NICE recommendations regarding screening for hepatitis B and C in patients at increased risk of infection⁴

Monitoring until patient is stabilised

FBC (incl differential WBC) every 2 weeks for the first two months³. Subsequently the interval between checks can be extended provided there is no cause for concern²

Ongoing Monitoring

The interval between FBC checks can be gradually extended from 2 weekly in patients taking doses less than 35mg/kg body weight, provided there is no cause for concern. The interval should not exceed 3-monthly^{2,3}
Serum creatinine, uric acid and LFTs should also be monitored^{1,2} 

Action required if abnormal results

If WBC < 2.5, or platelets < 100 therapy should be stopped and counts rechecked after 3 days¹

Additional notes

Patients should be examined for evidence of malignancy every 6 months and females should be advised to attend (when called) for routine cervical smears²

Significant drug interactions

- Antipsychotics (clozapine)
- Antivirals (didanosine, stavudine)

References

1. Summary of Product Characteristics for Hydrea Caps 500mg (hydroxycarbamide).
1. Date of revision of the text May 2012.
2. British Association Dermatologists – Clinical Guideline on management of psoriasis (2006)
3. Summary of Product Characteristics for Siklos 1000mg tablets (hydroxycarbamide). Date of revision of the text October 2012.
4. NICE public health guidance 43: Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (2012)

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

Hydroxychloroquine

Tests prior to starting treatment

FBC^{1,3}

U&Es^{1,2,3,4}

LFTs^{1,2,3,4}

Ask patient about visual impairment (not corrected by glasses).^{1,2,,3,4}

Record near visual acuity using a standard reading chart (with reading glasses if worn)^{1,2,3,4}


Monitoring until patient is stabilised

None identified

Ongoing monitoring

Monitor visual acuity annually using the standard reading chart.^{1, 2 ,3,4}

Ask patient about any other visual symptoms annually^{1,2,3,4}

If long term treatment is required (more than 5 years) individual arrangement should be agreed with local ophthalmologist^{1,2,3} 

Action required if abnormal results

Adjust dose if impaired renal or liver function²

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.^{1,2,3,4}

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.^{1,2,4}

Additional notes

To avoid excessive dosage in obese patients the dose should be calculated on basis of ideal body weight²

Significant drug interactions

- Anti-arrhythmics (amiodarone)
- Anti-bacterials (moxifloxacin)
- Antimalarials (artemether/lumefantrine)
- Mefloquine)
- Antipsychotics (droperidol)
- Cardiac glycosides (digoxin)
- Ciclosporin

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

References

1. BSR and BHPR guideline for disease-modifying anti-rheumatic drug therapy (DMARD) in consultation with the British Association of Dermatologists (2008).
2. BNF Issue 64.
3. Quick reference guideline for monitoring of DMARD therapy. To accompany BSR and BHPR guideline for DMARDs – April 2008. Nov 2009
4. Hydroxychloroquine and ocular toxicity recommendations on screening October 2009. The Royal College of Ophthalmologists

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

Leflunomide

Tests prior to starting treatment

Treatment should be initiated and supervised by rheumatology specialists (SPC)

FBC^{1,2}

U&Es^{1,2}

renal function^{1,2}

LFTs^{1,2}

BP on 2 occasions 2 weeks apart (if > 140/90 treat before commencing leflunomide)

Body weight^{1,2}

Monitoring until patient is stabilised

FBC and LFTs every month for the first 6 months.^{1,2}

BP and weight at each monitoring visit.^{1,2}

BNF recommends FBC (incl differential WBC and platelets) and LFTS every 2 weeks for first 6 months³

Ongoing monitoring

FBC, LFTs every two months if stable but at least every month if taking another immunosuppressant or potentially hepatotoxic drug.^{1,2,3}

BP and weight should be checked at each monitoring visit.^{1,2}

Action required if abnormal results

Withhold until discussion with rheumatologist if any of the following occur (falling trends may also prompt discussion):

- WBC < $3.5 \times 10^9/L$
- Neutrophils < $2 \times 10^9/L$
- Platelets < $150 \times 10^9/L$
- ALT or AST > 2-fold increase above upper limit of normal range¹

Withhold until discussion with rheumatologist if¹:

- Rash or itch,
- Hair loss,
- Severe sore throat/abnormal bruising (check FBC immediately)
- Hypertension (BP > 140/90) despite standard anti-hypertensives,
- Breathlessness,
- Unexplained weight loss > 10%¹
- Headache (severe or persistent)
- GI- upset (nausea, diarrhoea)

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

Significant drug interactions

- Methotrexate
- Live vaccines

References

1. BSR and BHPR guideline for disease-modifying anti-rheumatic drug therapy (DMARD) in consultation with the British Association of Dermatologists (2008).
2. BSR/BHPR [Quick reference guideline for monitoring of DMARD therapy](#) (November 2009)
3. BNF Issue 66.

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

Lithium

Tests prior to starting treatment

Renal function and U&Es (DTB recommends particular attention to Na and creatinine⁴) TFTs^{1,3,4}

Cardiac function (ECG recommended for patients with risk factors for, or existing CVD)¹

Baseline measurement of weight is desirable¹

Lithium level if switching from another brand/ preparation³

In bipolar disorder NICE suggest the following baseline monitoring: U&Es and serum creatinine, TFTs, FBC (if clinically indicated), ECG (for patients with CVD or risk factors for it), weight, height⁷

Additionally, as part an annual review of physical health, NICE recommend that patients with bipolar disorder have baseline lipid profile, plasma glucose levels and BP measured⁷

Monitoring until patient is stabilised


Plasma levels

NICE recommend levels checked one week after starting and one week after every dose change 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 impairment⁷). Levels should be monitored weekly until stable.

SLAM recommend measurement of plasma drug levels after at least 3-4 days, then 3-4 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 mania¹

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 good⁴.

Best Practice series recommends level after 3-4 days but within 7 days after starting therapy or changing dose⁸. A target of 0.6-1.0 mmol/L is recommended for most adult, non-elderly patients and 0.4-0.8 mmol/L for most elderly patients. Patients managed specifically outside of these ranges should be individually identified and the reason for the decision clearly documented in patient records⁸.

BNF recommends checking levels weekly after initiation and after each dose change until the dose has remained constant for 4 weeks. The recommended target serum-lithium concentrations are 0.4–1 mmol/L (lower end of the range for maintenance therapy and elderly patients) and 0.8–1 mmol/L for acute episodes of mania, and for patients who have previously relapsed or have sub-syndromal symptoms.² 

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NICE suggest that in bipolar disorder after 6 months the following monitoring should be carried out: TFTs, renal function (sooner if there is evidence of deterioration or patient starts drugs such as ACEIs, diuretics or NSAIDs) , FBC (only if clinically indicated), weight (if patient has gained weight rapidly)

Ongoing Monitoring

Thyroid monitoring

NICE, BNF and SLAM recommend TFTs every 6 months^{1,2,7} (more often if there is evidence of deterioration²)

UK Guidelines suggest every 6-12 months during treatment⁶

Best Practice review series recommends every 6 months during initial years of treatment decreasing to annually if stable⁸

DTB advises every 12 months unless there is evidence of affective relapse or clinical features of hypothyroidism⁴

Renal function

NICE, BNF and SLAM recommend checking renal function every 6 months^{1,2,7} (more often if evidence of impairment and/or deterioration, or the patient has other risk factors, such as starting ACEI, NSAIDs or diuretics)

Best Practice review series recommends every 12 months and in conjunction with any unexplained rise in lithium levels⁸

Plasma levels

NICE, BNF and Best Practice series recommend monitoring levels every 3 months once stable^{2,7,8} SLAM also recommend every 3 months, but state that every 6 months may be adequate in physically healthy young adults¹.

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 good⁴.

Priadel SPC states that the period between subsequent measurements can be increased gradually following stabilisation, but should not normally exceed 2-3 months³.

Increase frequency of monitoring if problems are suspected, the patient is elderly (over 65 years) or is co-prescribed an interacting drug^{1,4}

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 intake². Priadel SPC also recommends additional monitoring when there are signs of manic or depressive relapse, or lithium toxicity³.

Other monitoring

DTB recommends annual calcium checks⁴.

NICE and SLAM recommend monitoring weight/BMI^{1,7}, especially in patients with rapid weight gain.⁷ FBC should be checked if clinically indicated⁷.

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Additionally NICE recommend that all patients with bipolar disorder should have blood glucose, lipid profile (if over 40 years), BP and weight recorded as part of an annual physical health review⁷

Action required if abnormal results

Plasma levels

nGMS states serum lithium levels should be maintained between 0.6 and 0.8 mmol/l in patients who are prescribed it for the first time. A trial of at least six months with serum lithium levels between 0.8 and 1.0 mmol/l should be considered for patients who have relapsed previously while taking lithium or who still have sub-threshold symptoms with functional impairment.⁵

Serum lithium level range depends on whether taken once or twice daily and whether level measured at 12 or 24 hours³

Toxic effects reliably occur at levels $>1.5\text{mmol/L}$ ¹. 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 treatment².

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)⁷

If urea and creatinine levels become elevated, initiate closer monitoring of dose and blood levels and assess the rate of renal function deterioration⁷.

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 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 mU/L more frequent monitoring is indicated and a trial of levothyroxine may be appropriate particularly if the patient is symptomatic.⁹

Additional notes

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.^{2,9} 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 item⁹. Systems to identify and deal with medicines that might adversely interact with lithium therapy should be in place⁹.

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

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preparation¹. 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 noted⁴
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.⁷

Patients should be advised to:
maintain adequate fluid intake⁷, avoid dietary changes which reduce or increase sodium intake², seek medical attention if they develop diarrhoea and/or vomiting⁷, report the signs and symptoms of lithium toxicity, hypothyroidism, renal dysfunction and benign intracranial hypertension.²

NICE recommend that patients are monitored for signs of neurotoxicity which can occur at therapeutic levels⁷

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.¹

The following measures are QOF indicators for 2013/14⁵:

- 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 number of patients with bipolar disorder (and schizophrenia and other psychoses) who have had BP, total cholesterol: hdl ratio, blood glucose or HbA1c, BMI and alcohol consumption measured within the previous 12 months are QOF indicators for 2013/14.

Significant drug interactions

- ACE inhibitors
- Analgesics (all NSAIDs, ketorolac)
- Angiotensin II receptor antagonists
- Anti-arrhythmics (amiodarone)
- Antidepressants (SSRIs)
- Cytotoxics (arsenic trioxide)
- Dapoxetine
- Diuretics (acetazolamide, loop diuretics, thiazide and related diuretics, potassium sparing diuretics and aldosterone antagonists)
- Methyl dopa

Patients taking lithium should be warned not to take OTC NSAIDs⁷.

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)


References

1. The South London and Maudsley NHS Foundation Trust and Oxleas NHS Foundation Trust Prescribing Guidelines in Psychiatry (11th edition)
2. BNF Issue No 64
3. 3 Summary of Product Characteristics for Priadel 400mg prolonged-release tablets, Date of revision of text November 2013
4. Using lithium safely DTB 1999, 37, 3
5. 2013/14 general medical services (GMS) contract quality and outcomes framework (QOF) <http://www.nhsemployers.org/Aboutus/Publications/Documents/qof-2013-14.pdf> Revisions to the GMS Contract 2006/7
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 (Jul 2006)
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)

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Mercaptopurine

Tests prior to starting treatment

FBC¹
LFTs¹
U&Es including creatinine¹
TPMT assay¹ 

Consider NICE recommendations regarding screening for hepatitis B and C in patients at increased risk of infection⁶

Baseline HIV status should be established in those with risk factors⁴

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) for patients taking azathioprine² (the pro-drug of mercaptopurine).

IN GASTROENTEROLOGY

BSG state that there is no evidence to support weekly monitoring as described above. FBC every 2 to 4 weeks for 2 months and then every 4 to 8 weeks is considered fairly common practice³

Ongoing monitoring

IN GENERAL

BNF recommend a minimum of 3-monthly FBC monitoring for azathioprine (the pro-drug of mercaptopurine).²

BSR recommend that LFTs should also be monitored 3-monthly., and that monitoring of FBC and LFTs should continue at monthly intervals at a minimum if the patient is heterozygote for TPMT.

U&Es and creatinine should be monitored every 6 months¹

IN GASTROENTEROLGY

BSG suggest monitoring FBC every 4 to 8 weeks³

Action required if abnormal results

BSR advise that treatment *with azathioprine* should be withheld until discussion with consultant specialist if:¹

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- WBC < 3.5 x 10⁹/l,
- Neutrophils < 2 x 10⁹/l
- Platelets < 150 x 10⁹/l,
- AST, ALT increase to > twice the upper limit of normal
- Rash or oral ulceration occurs.¹
- abnormal bruising or severe sore throat occurs (withhold until FBC available)

If MCV > 105fl: check B12 , serum folate and TSH – withhold until results are available and discuss with specialist¹

Additional notes

Pneumococcal vaccine and annual flu vaccine should be given, but live vaccines should be avoided⁵.

In patients exposed to chickenpox or shingles, passive immunisation should be carried out using VZIG¹.

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

Sunscreens and protective clothing should be encouraged to reduce sunlight exposure¹

Significant drug interactions

- Allopurinol (reduce dose to one quarter)
- Antibacterials (co-trimoxazole and trimethoprim)
- Anticoagulants (coumarins)
- Clozapine
- Febuxostat

References

1. BSR and BHPR guideline for disease-modifying anti-rheumatic drug therapy (DMARD) in consultation with the British Association of Dermatologists. (2008)
2. BNF Issue 65 (March-September 2013)
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 (2012) Crohn's disease: management in adults, children and young people (CG152)
6. NICE public health guidance 43 (2012): Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

Mesalazine

Tests prior to starting treatment

U&Es^{1,2}

Renal function should be assessed prior to starting treatment^{1,2}

Monitoring until patient is stabilised

U&Es monitored at 3 months^{1,2}

Ongoing monitoring

U&Es monitored annually^{1,2}.

BSG support annual assessment of renal function as being sensible³

Action required if abnormal results

More frequent monitoring is required in renal impairment, with the frequency depending on individual patient history.^{1,2}

BSG recommends to stop therapy if renal function deteriorates³

Significant drug interactions

- Methotrexate
- Live vaccines

References

1. BNF Issue 64
2. Summary of Product Characteristics for Asacol® 400mg MR Tablets (mesalazine). (June 2010).
3. BSG Guidelines for the management of inflammatory bowel disease in adults(2011) – Gut2011, 60(5): 571-607

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Methotrexate

Tests prior to starting treatment

FBC, LFTs, U&Es, creatinine, chest X-ray (unless done in last 6 months). Pulmonary function tests should be considered in selected patients (e.g. abnormal shadowing on CXR)¹

BSG suggest FBC and LFTs when used to treat IBD⁸

Consider NICE recommendations regarding screening for hepatitis B and C in patients at increased risk of infection¹¹

Monitoring until patient is stabilised

IN GENERAL

BNF recommends FBC, renal and liver function every 1-2 weeks until therapy is stabilised.

RHEUMATOLOGY

FBC, U&Es and LFTs every 2 weeks until dose and monitoring has been stable for 6 weeks; thereafter monthly until the dose and disease is stable for 12 months.^{1, 5}

DERMATOLOGY

FBC, U&Es, creatinine and LFTs weekly and gradually increase interval until therapy stabilised^{1, 3, 5, 6}

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 month⁸

Ongoing monitoring

IN GENERAL

CSM, BNF and CKS recommend FBC, U&Es, renal function and LFTs every 2-3 months once stabilised^{3, 4, 5}


Best Practice series recommends every 1-2 months⁶

RHEUMATOLOGY

FBC, U&Es and LFTs every month until the dose and disease is stable for 12 months – thereafter the monitoring may be reduced in frequency based on clinical judgement with due consideration for risk factors including age, comorbidity, renal impairment etc when monthly monitoring should continue¹. Additionally the NPSA suggest that CRP, ESR or PV may be monitored every 3 months and creatinine every 3-6 months⁷. BSR note that the role of type III procollagen (PIIINP) (a marker of hepatic fibrosis) in the background of inflammatory arthritis remains unclear and is not recommended¹

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DERMATOLOGY

FBC, U&Es, creatinine and LFTs every 2-3 months once patient is stabilised¹
Best Practice series recommends that when used in patients with psoriasis monitoring of PIIINP every 2-3 months is available⁶. BAD also state that monitoring of PIIINP is recommended for early detection of liver disease¹ 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 time¹⁰ 

GASTROENTEROLOGY

BSG suggest that FBC and LFTs should be checked every month when used to treat IBD⁸

Action required if abnormal results

BSR recommend that treatment be withheld until discussion with consultant specialist if:¹

- WBC $< 3.5 \times 10^9/L$
- neutrophils $< 2 \times 10^9/L$
- platelets $< 150 \times 10^9/L$,
- AST, ALT increase to $>$ twice the upper limit of normal
- there is an unexplained fall in albumin (in the absence of active disease),
- rash or oral ulceration, nausea and vomiting, diarrhoea occurs
- there is new/ increasing dyspnoea or cough (discuss urgently with the specialist team)
- MCV $> 105fl$ (investigate and if B12 or folate low start appropriate supplementation)
- the patient develops mild to moderate impairment of renal function
abnormal bruising or severe sore throat occurs (withhold until FBC available)

Additional notes

Ask about abnormal bruising and monitor for symptoms of pneumonitis at each visit.²

Annual flu vaccine should be given, but live vaccines should be avoided.¹

In patients exposed to chickenpox or shingles, passive immunisation should be carried out using VZIG¹

Warn patients about risk of pneumonitis and advise them to seek medical attention if they develop symptoms such as dyspnoea, dry non-productive cough or fever.²

Patients should be advised to report all symptoms and signs suggestive of infection, especially sore throat^{3,8}


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Patients should be advised to stay well within the national recommendations on alcohol intake¹

In the event of suspected methotrexate-induced pneumonitis, withdraw treatment and administer corticosteroids¹.

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 ⁹

Significant drug interactions

- Anaesthetics (nitrous oxide)
- Analgesics (aspirin and NSAIDS- aspirin, diclofenac, ibuprofen, indometacin, ketoprofen, meloxicam and naproxen.) *Note, however the BSR state that a clinically significant interaction between NSAID and methotrexate is rare.* 
- Antibacterials (co-trimoxazole, trimethoprim)
- Antimalarials (pyrimethamine)
- Antipsychotics (clozapine)
- Ciclosporin
- Cytotoxics (cisplatin)
- Leflunomide
- Probenecid
- Retinoids (acitretin)

References

1. BSR & BHPR Guideline for disease modifying anti-rheumatic drug therapy (DMARD) in consultation with the British Association of Dermatologists (2008)
2. Current problems in pharmacovigilance. Sept 2003 Vol 29 p 5
3. BNF Issue 65 (March-September 2013)
4. Current Problems in Pharmacovigilance Sept 1997, Vol 23, 12
5. CKS Clinical Topic: DMARDs (last revised January 2013)
6. 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

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Minocycline

Tests prior to starting treatment

LFTs¹

Monitoring until patient is stabilised

None identified

Ongoing monitoring

If treatment continued for longer than 6 months: Monitor LFTs every 3 months¹.

Watch for hazardous idiosyncratic hypersensitivity reactions e.g. eosinophilia, pneumonitis and nephritis, autoimmune hepatitis and lupus erythematosus-like syndrome.

Action required if abnormal results

Discontinue if the patient develops hepatotoxicity, pigmentation or SLE, or if pre-existing SLE gets worse.¹

Additional notes

NICE has questioned the ongoing use of minocycline in view of safety concerns, lack of evidence of benefit over alternative treatments and relatively high acquisition cost.²

Significant drug interactions

- Anticoagulants (warfarin, phenindione)
- Retinoids

References

1. BNF Issue 65
2. NICE. Key therapeutic topics – Minocycline, evidence context (2013). Accessible via: <http://publications.nice.org.uk/minocycline-ktt11/evidence-context>

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Mycophenolate

Tests prior to starting treatment

FBC, U&E, LFT & CXR¹

Monitoring until patient is stabilised

FBC every week for 4 weeks then twice a month for 2 months.^{1,2,4}

FBC/LFTs/U&Es fortnightly for the first 2 months. Then once a month for 4 months.³

Ongoing monitoring

FBC every month in the first year even after patient stabilised on treatment.^{1,2,4}

FBC/LFTs/U&Es every 3 months thereafter (ie after 6 months see above).³

Action required if abnormal results

If WBC < 3.5 x 10⁹/L; Neutrophils < 2.0 x 10⁹/L; Platelets < 150 x 10⁹/L - withhold until discussed with specialist team.^{1,3}

If neutrophils < 1.3 x 10⁹/L, manufacturer advises to interrupt or discontinue therapy.⁴

If MCV > 105 fL - withhold and check vitamin B12, folate and TSH. If abnormal, treat any underlying abnormality. If normal, discuss with the specialist team.³

If AST, ALT > twice upper limit of reference range. Unexplained decrease in albumin (in absence of active disease) - withhold until discussed with specialist team.³

If mild-to-moderate renal impairment† - withhold until discussed with specialist team.³

Additional notes

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

Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding.²

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

If severe sore throat, abnormal bruising – withhold until FBC result is available and discuss with specialist team.³

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

Significant drug interactions

- Antibacterials - rifampicin

References

1. Chakravarty, K., McDonald, H., Pullar, T. et al. (2008) BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. *Rheumatology* 47(6), 924-925.
2. BNF 66 (September 2013)
3. CKS: DMARDs (Last revised in January 2013)
4. SPC for mycophenolate (Cellcept™; Roche). Date of revision: July 2013

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

NSAIDs (including COX II)

Tests prior to starting treatment

For daily NSAID use in patients with risk factors for GI bleeding: baseline haemoglobin or haematocrit³. (factors that increase risk of gastrointestinal bleeding are defined as any of the following: age \geq 75, peptic ulcer disease, history of gastrointestinal bleeding, or glucocorticoid use).³

For daily NSAID use in patients with risk factors for developing renal insufficiency: baseline creatinine³ (risk factors for renal insufficiency are defined as any of the following: age \geq 75, diabetes mellitus, hypertension, angiotensin converting enzyme (ACE) inhibitor use or diuretic use).³

Monitoring until patient is stabilised

For patients with heart failure:

All NSAIDs are contra-indicated in patients with severe heart failure and diclofenac, celecoxib and etoricoxib are contraindicated in patients with any degree of heart failure⁴

For patients with mild-to-moderate heart failure

Monitor weight, jugular venous distension, crepitations, hepatomegaly, ascites, and peripheral oedema 1–2 weeks after starting or increasing NSAID dose. Consider monitoring U&Es 1–2 weeks after starting or increasing NSAID dose, particularly in people taking an ACE inhibitor, an angiotensin-II receptor antagonist, a diuretic, or in those with impaired renal function.²

For patients with hypertension:

Monitor BP 2–4 weeks after starting or increasing dose. Etoricoxib — check BP within 2 weeks of starting and periodically thereafter.²

For patients with renal impairment:

Monitor U&Es 1–2 weeks after starting or increasing NSAID dose then regularly thereafter.²

For patients with risk factors for developing renal insufficiency (see above):

Monitor creatinine within the first 3 months.³

For hepatic impairment:

Enquire about adverse effects.²

Ongoing monitoring

For daily NSAID use with risk factors for GI bleeding (see above): haemoglobin or haematocrit after one year of treatment.³

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For daily NSAIDs and risk factors for developing renal insufficiency (see above): creatinine should be assessed at least annually.³

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.¹

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

Significant drug interactions

(Interactions generally do not apply to topical NSAIDs, see BNF appendix 1 for more details)

- Analgesics (concomitant NSAIDs or aspirin, ketorolac)
- Antibacterials (quinolones)
- Anticoagulants (coumarins, dabigatran, phenindione, heparins).
- Antidepressants (SSRI, venlafaxine)
- Antidiabetics (sulphonylureas).
- Antivirals (ritonavir).
- Ciclosporin.
- Cytotoxics (methotrexate – see monitoring methotrexate entry above, erlotinib)
- Dimethyl sulfoxide
- Diuretics (triamterene)
- Lithium
- Pentoxifylline
- Probenecid
- Tacrolimus.

References

1. BNF 66 (September 2013- March 2014)
2. CKS: NSAIDs. Last revised in January 2013
3. American College of Rheumatology. Drug safety alert: <http://www.rheumatology.org/Practice/Clinical/Quality/Drug-Safety/>
4. MHRA: Diclofenac: new contraindications and warnings after a Europe-wide review of cardiovascular safety (June 2013). Accessed via <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON286975>

A significant drug interaction is one given black dot status in the BNF i.e. those that are potentially serious and where concomitant administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)

Phenytoin

Tests prior to starting treatment

LFTs and FBC²

Monitoring until patient is stabilised

SPC suggests frequent FBC throughout treatment¹ but BNF states that evidence of practical value is unsatisfactory³

Drug monitoring in patients with epilepsy should NOT be routinely performed unless to assess adherence or suspected toxicity or after adjustment of phenytoin dose^{2,4}
However where monitoring is felt to be necessary, dosage should be adjusted according to serum levels where assay facilities exist.¹

Ongoing monitoring

SPC suggests frequent FBC throughout treatment¹ but BNF states that practical value is unsatisfactory³

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 drugs²

SIGN suggest that liver function and full blood count should not be monitored routinely and there is no indication for routine monitoring of drug levels⁴

Serum folate at least 6 monthly¹ but again this is not supported by NICE, SIGN or BNF.^{2,3,4}

Action required if abnormal results

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

Asymptomatic minor abnormalities in test results are not necessarily an indication for changes in medication²

Folic acid supplements to be initiated where necessary.¹

Additional notes

Therapeutic serum level 10-20µg/ml although some cases of tonic clonic seizures may be controlled with lower serum levels¹

Phenytoin is highly protein bound and where protein binding is reduced, as in uraemia, total phenytoin levels will be reduced accordingly. Under these

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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 toxicity¹

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.¹

Phenytoin may affect blood sugar metabolism tests¹ (no additional data provided)

Patients/carers should be told how to recognise signs of blood or skin disorders³. If rash occurs phenytoin should be discontinued, if it is mild it can be reintroduced cautiously but discontinue immediately if recurrence³

Significant drug interactions

- Acetazolamide
- Analgesics (NSAIDs)
- Anti-arrhythmics (amiodarone, dronedarone).
- Antibacterials (chloramphenicol, rifamycins, telithromycin, trimethoprim)
- Anticoagulants (coumarins)
- Antidepressants (fluoxetine, fluvoxamine, mianserin, SSRIs, St John's wort, tricyclics & tricyclic-related antidepressants).
- Antiepileptics (ethosuximide, stripentol, topiramate, perampneniel)
- Antifungals (itraconazole, ketoconazole, miconazole, fluconazole, voriconazole, posaconazole)
- Antimalarials (mefloquine, pyrimethamine)
- Antipsychotics (aripiprazole)
- Antivirals (boceprevir, rilpivirine, telaprevir, indinavir, elvitegravir)
- Calcium channel blockers (diltiazem)
- Ciclosporin
- Corticosteroids
- Cytotoxics (cabazitaxel, lapatinib, imatinib)
- Disulfiram
- Diuretics (eplerenone)
- Ivacaftor
- Oestrogens Progestogens
- Orlistat
- Sulfinpyrazone
- Theophylline
- Ulcer healing drugs (cimetidine, esomeprazole, sucralfate)
- Ulipristal

References

- 1 Epanutin capsules SPC (revised March 2012)
- 2 NICE Clinical Guideline CG137 (The epilepsies: diagnosis and management of the epilepsies in adults in primary and secondary care) (2012)
- 3 BNF Issue 65
- 4 SIGN Guideline No 70- Diagnosis and management of epilepsy in adults (April 2003) (updated 2005)

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D-Penicillamine

Tests prior to starting treatment

FBC including platelets
urinalysis for blood disorders and proteinuria,
U&Es and creatinine^{1,2,3}

Monitoring until patient is stabilised

Urinalysis for protein/ blood and FBC every 2 weeks until on a stable dose for 3 months^{1,3}

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 increase²

Ongoing monitoring

Urinalysis for protein/blood and FBC every month^{1, 3, .4}

Action required if abnormal results

Withhold treatment until discussion with rheumatologist if WBC<3.5, neutrophils<2.0, platelets<150l^{1,3}

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^{2,4}

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.^{1,3}

Proteinuria, associated with immune complex nephritis, occurs in up to 30% of patients but may resolve despite continuation of treatment and treatment may be continued provided renal function tests remain normal, oedema is absent and 24 hour urinary excretion does not exceed 2g²

If abnormal bruising or sore throat- withhold until FBC available^{1,3}

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.^{1,3}

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.²

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Patients who are hypersensitive to penicillin may react rarely to penicillamine.²
Longer intervals for blood counts and urine tests may be adequate in cystinuria.^{1,2,3}
Alteration of taste may settle spontaneously.^{1,3}
Especially careful monitoring is necessary in the elderly since increased toxicity has been observed in this patient population regardless of renal function.⁴

Significant drug interactions

- Clozapine

References

1. BSR/BHPR Guideline for disease modifying anti-rheumatic drug therapy (DMARD) in consultation with the British Association of Dermatologists (2008)
2. BNF. March –September 2013; Issue 65
3. CKS – DMARDs. Last revised January 2013
4. SPC for D-penicillamine (Distamine™ tablets). Last revised November 2012

Pioglitazone

Tests prior to starting treatment

Contraindications for the use of pioglitazone include: ^{1, 2}

- (i) cardiac failure or a history of cardiac failure (NYHA stages I to IV)
- (ii) current bladder cancer or a history of bladder cancer^{1, 2, 4}
- (iii) uninvestigated macroscopic haematuria


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


Liver function: LFTs^{1,2}.
Weight ¹

Monitoring until patient is stabilised

LFTs should be monitored periodically based on clinical judgement^{1,2}

Ongoing monitoring

LFTs should be monitored periodically based on clinical judgement and must be checked if patient develops signs suggesting liver dysfunction.^{1, 2} 

Weight should be closely monitored ¹ 

Patients should be observed for signs and symptoms of heart failure, weight gain or oedema; particularly those with reduced cardiac reserve¹.

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

Investigate any macroscopic haematuria before starting pioglitazone therapy¹

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.^{1,2}

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 ¹

If jaundice is observed therapy should be discontinued. ¹

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Additional notes

Advise patients to seek immediate medical attention if symptoms such as nausea, vomiting, abdominal pain, fatigue and dark urine develop³

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^{1,2}

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 treated⁴.

Significant drug interactions

No potentially serious drug interactions are listed in BNF 66 for pioglitazone.

References

1. Summary of Product Characteristics (SPC) for Actos (date of revision of text November 2013),
2. BNF Issue 66
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>

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Propylthiouracil

Tests prior to starting treatment

Specialist Initiation only¹

TFTs^{1,3}

WBC⁴

LFTs⁹

Monitoring until patient is stabilised

UK Guidelines recommend TFTs every 1-3 months until stable³.

TFTs after first 3 months of treatment¹

Monitor for signs and symptoms of liver injury, especially during the first 6 months after initiation of therapy⁸.

Ongoing Monitoring

UK Guidelines recommend annual TFT monitoring once stable if being used as a long-term treatment option³

Action required if abnormal results

Repeat WBC if patient develops fever, mouth ulcers, sore throat or other symptoms of infection⁴

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

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.⁶ Provide supportive care⁸.

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 infection²

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. Liver function tests including bilirubin, ALP, and transaminases should be obtained.^{5,7}

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Significant drug interactions

None noted

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 Issue 66, September 2013
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: Monitoring during and after carbimazole or propylthiouracil treatment. Last revised June 2013. Available at <http://cks.nice.org.uk/hyperthyroidism#!scenariorecommendation:3>

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Rivaroxaban

Tests prior to starting treatment

Clotting screen, U&E's, LFTs, FBC²

BP⁶ 

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.²

Ongoing Monitoring

U&E's, LFTs, FBC at least once a year.²

Repeat U&E's every 6 months if CrCl 30–60 mL/min or every 3 months if CrCl 15–30 mL/min.²

More frequent U&E's/LFTs advised if intercurrent illness that may impact renal or hepatic function.²

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.²

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.⁴

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

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.³

Rivaroxaban should ideally be stopped 24 hours prior to surgery if possible⁵

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Significant drug interactions

- Analgesics – diclofenac, ketorolac
- Anticoagulants – apixaban, dabigatran
- Antifungals – ketoconazole
- Antivirals - ritonavir

References

1. BNF 66 (September 2013- March 2014)
2. CKS: Anticoagulation – oral. May 2013
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 25/02/2014
5. SPC for rivaroxaban – last updated Nov 2013

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Sirolimus

Tests prior to starting treatment

Renal function (serum creatinine), liver function, lipid levels and BP ^{1,2}

Consider NICE recommendations regarding screening for hepatitis B and C in patients at increased risk of infection ³

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).^{1,2} 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.⁴ Therapeutic drug monitoring is also necessary after changes in the dose of sirolimus or ciclosporin, or of their relative timing.^{4,5}

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) ^{1,2}

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

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


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

Ongoing Monitoring

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

The BNF advises monitoring lipids²; the UK Renal Association recommends that this is done on an annual basis in all renal transplant recipients.⁶

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.⁶

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

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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.^{1,2}

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

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

New onset diabetes after transplant should be managed according to local unit protocol.⁶

Additional notes

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

Significant drug interactions

- Antibacterials (clarithromycin, erythromycin, telithromycin, rifabutin, rifampicin)
- Antifungals (itraconazole, ketoconazole, miconazole, voriconazole)
- Antivirals (atazanavir, boceprevir, telaprevir)
- Crizotinib
- Diltiazem
- Grapefruit juice
- Verapamil

Close monitoring of whole blood-sirolimus concentration is required during concomitant treatment with potent inducers or inhibitors of metabolism and after discontinuing them, or if the dose of ciclosporin is reduced significantly or stopped.²

References

1. Summary of Product Characteristics for sirolimus. Date of revision of text August 2013.
2. BNF Issue 66
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. Stenton SB, et al. [Sirolimus: the evidence for clinical pharmacokinetic monitoring](#). Clin Pharmacokinet 2005; 44: 769–86.
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6. Ther Drug Monit 2006; 28: 720–5. [PubMed](#)
7. UK Renal Association (2011) Post-operative Care of the Kidney Transplant Recipient – 5th edition http://www.renal.org/Libraries/Guidelines/Post-operative_care_of_the_kidney_transplant_recipient_-_Final_Version-_05_February_2011.sflb.ashx

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Statins

Tests prior to starting treatment

Baseline lipid profile^{1,7,11} Two lipid measurements — at least one fasting lipid sample taken to measure total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides,¹¹

LFTs^{1,2,3,4,5,6,7}

U&Es paying particular attention to creatinine if using rosuvastatin,⁴

Thyroid function (see additional notes)^{2,3,4,11,5,6,7,11}

CPK levels recommended in patients with pre-disposing factors for rhabdomyolysis: (renal impairment, female, untreated hypothyroidism, personal or family history of muscular disorders, previous history of muscular toxicity with another statin or fibrate, alcohol abuse or aged > 65 years)^{1,2,3,4,5,6,7,11}

Monitoring until patient is stabilised

LFTs within 1-3 months of starting treatment then at 6 month intervals for one year unless indicated sooner². SIGN recommend LFTs 12 weeks after starting treatment and after each dose increase and then periodically thereafter, however routine monitoring of LFTs is not supported by the available evidence. They also note that the preferred biochemical test to ascertain significant liver injury is bilirubin.

Simvastatin: SPC advises that LFTs should be monitored when clinically indicated but patients titrated to the 80mg dose should receive an additional test prior to titration, 3 months after titration to the 80mg dose, and periodically thereafter (e.g., semi-annually) for the first year of treatment.³

Atorvastatin SPC advises LFTs monitored before initiation of treatment and periodically thereafter⁵

Fluvastatin SPC advises 12 weeks after initiation or dose increase and periodically thereafter⁷.

Rosuvastatin: SPC advises LFTs should be monitored 3 months after initiation⁴, 40mg dose should only be initiated under specialist supervision and is contraindicated in Asian patients⁴

Ongoing monitoring

Routine monitoring of CPK levels in asymptomatic patients is not warranted, however CPK levels should be measured in patients with unexplained muscle pain, weakness or cramps.^{1,4,5,6}

Assessment of renal function should be considered during routine follow up of patients treated with 40mg rosuvastatin but this dose is contraindicated if creatinine clearance < 60 ml/min⁴

Action required if abnormal results

Statin therapy should not be started/ discontinued if ALT or AST >3x upper limit of normal (ULN)^{2,4,5,6}. Statins should be used with caution in those with a history of liver disease or with a high alcohol intake^{2,3,4,5,6}

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Therapy should not be started/ discontinued if CPK > 5x ULN or if muscular symptoms are severe and cause daily discomfort (even if CPK level ≤ 5x ULN).^{4, 5, 6, 7} Test should be repeated after 5-7 days^{4, 5, 6}

If symptoms resolve and CPK returns to normal, can consider re-introduction of therapy or alternative statin at lowest dose with close monitoring.^{4, 5, 6}

Statins should be discontinued in patients who develop peripheral neuropathy that may be attributable to the statin treatment, and further advice from a specialist should be sought.¹

Rosuvastatin is contra-indicated if creatinine clearance <30ml/min Maximum 40mg dose if less than 60ml/min⁴

Additional notes

Patients should be advised to report unexplained muscle pain.^{2,3,5,6,7,10}

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.^{2,3,4,5,7}

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 thyroxine⁹

Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (> 5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results³

Significant drug interactions

- Anti-arrhythmics (amiodarone when used with simvastatin) MHRA advise is that patients taking amiodarone should not take more than 20mg simvastatin daily and patients taking concomitant atorvastatin should have their lipid levels monitored to ensure lowest necessary dose of atorvastatin⁸)
- Antibacterials (simvastatin with erythromycin, clarithromycin or telithromycin, telithromycin-atorvastatin, daptomycin – any statin). MHRA advice⁸ is that combinations of potent CYP3A4 inhibitors and simvastatin such as erythromycin, clarithromycin or telithromycin are contraindicated and avoid in combining these agents with atorvastatin if possible.

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- If there is a need to co-prescribe then patients taking clarithromycin should not exceed atorvastatin 20mg daily.⁸
- Anticoagulants (coumarins – simvastatin or fluvastatin, rosuvastatin-phenindione or coumarins). MHRA advice is that patients taking warfarin/coumarins should have their INR measured before starting treatment with either simvastatin or atorvastatin and also regularly during treatment especially with dose changes. They also note that caution is particularly necessary with fluvastatin.
- Antifungals (simvastatin with itraconazole, ketoconazole posaconazole or miconazole itraconazole). Atorvastatin with itraconazole or posaconazole. MHRA advice⁸ is that combinations of simvastatin and itraconazole and ketoconazole are contraindicated and for atorvastatin consider temporary suspension of statin if the antifungal is to be taken for a short period and do not exceed 40mg atorvastatin daily in patients taking itraconazole agents and exercise caution in combining these agents with atorvastatin
- Antivirals (simvastatin with amprenavir, atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, or lopinavir) - MHRA advice⁸ is that combinations of HIV protease inhibitors and simvastatin are contraindicated and should be avoided with atorvastatin if possible. If a combination of atorvastatin and a protease inhibitor is required lipid levels should be monitored closely to ensure that the lowest possible dose of atorvastatin is used. They also advise that HIV protease inhibitors strongly increase exposure to rosuvastatin (unknown mechanism) are not recommended for combination use.
- Calcium-Channel Blockers (verapamil–simvastatin) MHRA advice is that patients taking verapamil should not take more than 20mg of verapamil or 40mg of diltizem daily. For patients taking either verapamil or diltiazem and concomitant atorvastatin they advise that lipid levels should be monitored to ensure the lowest necessary dose of atorvastatin is used.:
- Ciclosporin - MHRA advice⁸ is to not exceed simvastatin 10mg or atorvastatin 10mg daily in patients taking ciclosporin. They also note that caution is also needed with fluvastatin and that rosuvastatin is contraindicated.
- Danazol – MHRA advice is that patients taking danazol should not exceed 10mg simvastatin daily⁸
- Lipid-regulating drugs (gemfibrozil, fibrates, nicotinic acid) - MHRA advice⁸ is to not exceed simvastatin 10mg in patients taking fibrates (except fenofibrate) and to note that there is an increased risk of myopathy with both simvastatin and atorvastatin. For rosuvastatin they advise that patients taking fibrates should be started on a 5mg dose and should not take more than 20mg daily.
- Grapefruit juice - MHRA advice is to avoid grapefruit juice in patients taking simvastatin and limit intake to very small

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quantities (or avoid altogether)

in patients taking atorvastatin⁸

References

1. NICE. (Issue date: May 2007). MI: secondary prevention Secondary prevention in primary and secondary care for patients following a myocardial infarction.
2. BNF Issue 66 (September 2013).
3. Merck Sharp & Dohme Limited. *Summary of Product Characteristics of Simvastatin*. Last revised Nov 2013
4. AstraZeneca UK Limited. *Summary of Product Characteristics of Rosuvastatin*. Last revised May 2013
5. Pfizer Limited. *Summary of Product Characteristics of Atorvastatin*. Last revised June 2013
6. Bristol-Myers Squibb Pharmaceutical Limited. (17/05/2013). *Summary of Product Characteristics of Pravastatin*. Last revised May 2013
7. Novartis Pharmaceuticals UK Ltd. *Summary of Product Characteristics of Fluvastatin*. Last revised December 2013
8. MHRA. (January 2008). Statins: interactions, and updated advice for atorvastatin. *Drug Safety Update ; Vol 1, Issue 6: 2*
9. 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. Last accessed 24th Dec 2013.
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11. CKS. (December 2008). *Lipid modification - CVD prevention*. Available: <http://cks.nice.org.uk/lipid-modification-cvd-prevention>. Last accessed 24th Dec 2013.

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Tacrolimus

Tests prior to starting treatment

ECG, BP, FPG, U&Es (particularly potassium), liver and renal function tests, FBC, blood clotting values, plasma protein measurements.^{1,2}

Consider NICE recommendations regarding screening for hepatitis B and C in patients at increased risk of infection³

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 2-3 times weekly during the early post-transplant period.^{1,4} Clinical study analysis suggests that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20ng/ml.¹

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.^{1,2}

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 determinations.^{1,2}

Dermatology

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

Ongoing Monitoring

Blood levels: Whole blood trough levels should be monitored periodically during maintenance therapy (especially during episodes of diarrhoea)²

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.⁴

In renal transplant: In renal transplant the UK Renal Association recommends monitoring renal function (serum creatinine and urine protein excretion) and blood pressure at each renal clinic visit, and lipid monitoring annually in all renal transplant recipients. 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.⁴

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Action required if abnormal results

If hypertrophic changes occur, consider dose reduction or discontinuation.^{1,2}

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

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 (AHFS)

Additional notes

Patients should be informed that tacrolimus can cause diabetes and should be advised to see their clinician if they develop frequent urination or increased thirst or hunger.⁶

Excessive exposure to UV and sunlight should be avoided.² 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.⁴

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

The UK Renal Association recommends that renal transplant recipients receive the pneumococcal vaccine and one booster every five years, and annual influenza vaccine.⁴

Significant drug interactions

- Analgesics (ibuprofen)
- Antibacterials (clarithromycin, erythromycin, rifampicin, aminoglycosides, chloramphenicol, telithromycin)
- Anticoagulants (dabigatran)
- Antidepressants (St John's Wort)
- Antiepileptics (phenobarbital)
- Antifungals (fluconazole, itraconazole, ketoconazole, posaconazole, miconazole, voriconazole, amphotericin, caspofungin)
- Antipsychotics (droperidol)
- Antivirals (atazanavir, ritonavir, boceprevir, efavirenz, fosamprenavir, saquinavir, telaprevir)
- Calcium-channel blockers (diltiazem, nifedipine)
- Ciclosporin
- Cytotoxics (crizotinib)
- Diuretics (potassium-sparing diuretics and aldosterone antagonists)
- Grapefruit juice
- Potassium salts
- Ranolazine

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References

1. Summary Product Characteristics for tacrolimus (Adoport). Date of revision of text, May 2013
2. BNF Issue 66
3. NICE public health guidance 43: Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (2012)
UK Renal Association (2011) Post-operative Care of the Kidney Transplant Recipient – 5th edition http://www.renal.org/Libraries/Guidelines/Post-operative_care_of_the_kidney_transplant_recipient_-_Final_Version-05_February_2011.sflb.ashx
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. American Hospital Formulary Service 2013

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Theophylline/ aminophylline

Tests prior to starting treatment

U&Es (paying particular attention to potassium)^{2,3}
LFTs^{2,3}

Enquire about smoking status for patient, and advise patient to seek advice from doctor if status is likely to change¹.

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)⁴

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.⁴

Ongoing monitoring

Check plasma theophylline levels if-

- person experiences side effects that may suggest toxicity (nausea, vomiting, tremor or palpitations)^{5,6}
- After smoking cessation (more than 7 days) check theophylline Cp^{1,6}. This is not required in an acute situation where smoking is stopped for less than 7 days.¹

It is also advisable to recheck plasma levels every 6-12 months 

Note- Additional monitoring may be required in patients with congestive heart failure, chronic alcoholism, liver dysfunction or with viral infections due to reduced theophylline clearance.

Potassium levels: periodically in at risk patients^{2,3}

Reassess smoking status: Smoking may cause plasma concentration (Cp) reduction and stopping smoking may increase Cp^{2,3}

Monitor alcohol consumption as high levels of consumption can reduce plasma concentration of theophylline.^{2,3}

Action required if abnormal results

A lower dose may be required in patients with reduced hepatic function^{2,3}

Xanthines can potentiate hypokalaemia resulting from beta-2-agonist therapy steroids, diuretics and hypoxia. Particular caution is advised in severe asthma. It is recommended that serum potassium levels are monitored in such situations^{2,3}.

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Dose adjustments are product specific. Refer to relevant Summary of Product Characteristics

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/ litre⁴

BTS/SIGN advise checking levels during pregnancy as protein binding decreases, the free level of drug will increase. They particularly recommend checking levels in pregnant women with acute severe asthma and in those that are critically dependent on therapeutic theophylline levels.⁷

Significant drug interactions

- Antibacterials (ciprofloxacin, norfloxacin and other quinolones, clarithromycin, erythromycin,).
- Antidepressants (fluvoxamine, St John's Wort).
- Antiepileptics (phenobarbitone, phenytoin)
- Antifungals (fluconazole, ketoconazole).
- Antivirals (ritonavir).
- Calcium-channel blockers (verapamil).
- Desifarox
- Febuxostat
- Interferon alfa
- Ulcer-healing drugs (cimetidine).
- Rifampicin
- Lithium

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. Nuclin SA – Meda Pharmaceuticals. Date of revision of the text: November 2013.
3. Summary of Product Characteristics. Phyllocontin Continus. Date of revision of the text: July 2006.
4. BNF Issue 66
5. UK Medicines Information (UKMi). UKMi Q&A 136.4, Which medicines need dose adjustment when a patient stops smoking? August 2012. Accessed online via www.evidence.nhs.uk.
6. National Institute for Clinical Excellence. Clinical Knowledge Summaries – Asthma. June 2011. Accessed online via <http://cks.nice.org.uk/>
7. British Thoracic Society/ SIGN. British Guideline on the management of asthma (revised Jan 2012). Accessed online via <http://www.brit-thoracic.org.uk/Portals/0/Guidelines/AsthmaGuidelines/sign101%20Jan%202012.pdf>

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Thyroxine (levothyroxine)

Tests prior to starting treatment

TFTs.^{1,2}

UK guidance recommend TSH and FT4 as most important markers²

ECG.^{1,3,4}

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

Monitoring until patient is stabilised

UK guidance recommends that monitoring should not occur within two months of a dosage change as this is the minimum period required to achieve stable concentrations.^{1,2} However earlier consensus guidance recommends that TSH should be checked 6 weeks after initiation of thyroxine to see if dose adjustment required. (After 3-4 wks in the elderly, esp. if IHD present.)⁵

Ongoing monitoring

Recheck TFTs annually once patient has been stabilised.^{1,2}

Action required if abnormal results

If the TSH level is below the reference range or is undetectable, titrate the levothyroxine dose down in 25-microgram steps until the TSH level is within the reference range. This may be difficult in some people who have an apparent psychological benefit and general feeling of well-being when their TSH concentration is undetectable. Titrating down by 25 micrograms in each instance may make this reduction possible.¹

If the TSH is elevated, titrate the levothyroxine dose up in 25 microgram to 50 microgram increments until the TSH is within the reference range.¹

Additional notes

Pre-treatment ECG is considered valuable as changes induced by hypothyroidism may be confused with evidence of ischaemia.^{1,3}

Both TSH and FT4 should be measured in clinical situations where the pituitary–thyroid axis is not intact or is unstable, or if non-adherence or malabsorption is suspected. If the person has permanent secondary (central) hypothyroidism, TSH measurement is valueless and FT4 alone should be used for monitoring.¹

A change in requirement for thyroid hormone can occur with ageing.²

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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.⁶

Caution is recommended when prescribing thyroxine to patients with adrenal insufficiency, age >50 years, cardiovascular disorders.^{1,3}

Significant drug interactions

- Anticoagulants (coumarins, phenindione)

References

1. CKS. Hypothyroidism. Last revised in February 2011.
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; Amdipharm Mercury). Last revised October 2012
4. BNF Issue 65 (September 2013)
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)

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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.^{4,6}

LFTs, FBC (including platelet count, bleeding time and coagulation tests) and BMI^{1,2,5,6}

If used for bipolar disorder, NICE recommend TFTs, blood glucose, lipid profile (if over 40 years), weight and height.⁶


Monitoring until patient is stabilised

LFTs and PT periodically within first 6 months of treatment^{1,5}. 

Ongoing monitoring

FBC (including platelet count), bleeding time and coagulation tests are recommended before surgery⁴, and in cases of spontaneous bruising or bleeding¹

LFTs, FBC and BMI (in those who gain weight rapidly) after 6 months^{2,5,6}

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).^{4,6} 

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.⁷

As part of annual physical monitoring for patients with bipolar disorder NICE additionally recommend: TFTs (every 6 months if rapid-cycling but otherwise every 12 months), blood glucose, lipid profile (if over 40 years), weight and height.⁶

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^{1,5,6}

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.^{1,5}

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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.^{1,5,6}

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

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.^{1,3,5,6}

Significant drug interaction

- Antibacterials (pivmecillinam, carbapenems)
- Antidepressants (SSRIs, St John's wort, tricyclics and tricyclic-related antidepressants)
- Antiepileptics (lamotrigine)
- Antimalarials (mefloquine)
- Antipsychotics (olanzapine)
- Orlistat
- Ulcer-healing Drugs (cimetidine)


References

1. Summary of Product Characteristics for Epilim. Date of revision of the text December 2013
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: December 2013)
5. BNF Issue 66; September 2013
6. NICE Clinical Guideline 38: The management of bipolar disorder in adults, children and adolescents in primary and secondary care (Jul 2006)
7. Clinical Knowledge Service: Epilepsy (June 2009)

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Warfarin

Tests prior to starting treatment

PT¹
APTT¹
platelet count¹
LFTs¹
BP⁵ 
Thyroid status⁴.

(local practice may vary to also include FBC, U+E's and blood group and antibodies (aka Group and Save).

Monitoring until patient is stabilised

For rapid anticoagulation, BCSH guidelines recommend daily INR for a minimum of 4 days* until desired INR is achieved, then weekly until stable then frequency of follow-up can be extended.¹

*Initial frequency of INR testing may vary and in practice, first INR may not be measured until after 2 days of treatment (i.e on day 3) and then repeated on day 4

CKS recommend that once 2 consecutive INRs are within the therapeutic range the INR should be tested twice weekly for 1–2 weeks, followed by weekly measurements until at least two INR measurements are within the therapeutic range.⁴

Ongoing monitoring

12 weekly monitoring of INR is considered acceptable in patients stabilised on warfarin¹

But more frequent monitoring (e.g. every 1-2 weeks) of the INR may be advisable if the person has an increased risk of overcoagulation, has severe hypertension, liver disease (including alcoholic liver disease) or renal failure, is considered to be at increased risk of bleeding, or finds adherence difficult.⁴

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.²

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.¹

Action required if abnormal results

People with hypothyroidism or hyperthyroidism should be closely monitored on starting warfarin therapy⁴.

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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.⁵

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.¹
For $INR > 8$, oral anticoagulants should be stopped and advice sought from haematologist on management.¹

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.²

Additional notes

Refer to Appendix 1 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.³

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 ration (INR) results.⁴

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.⁴

Significant drug interactions

- Acitretin
- Alcohol
- Amiodarone
- Anabolic Steroids
- Antidepressants, SSRI
- Antidepressants, Tricyclic
- Apixaban
- Aspirin
- Azathioprine
- Azithromycin
- Aztreonam
- Carbamazepine
- Cephalosporins
- Chloramphenicol
- Cimetidine
- Clarithromycin
- Clopidogrel
- Colestyramine
- Corticosteroids
- Cranberry Juice
- Dabigatran
- Danazol
- Diclofenac
- Dipyridamole
- Disulfiram

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- Dronedaron
- Efavirenz
- Entacapone
- Enteral Foods
- Enzalutamide
- Erlotinib
- Erythromycin
- Esomeprazole
- Etoposide
- Fibrates
- Fluconazole
- Fluorouracil
- Flutamide
- Fluvastatin
- Gefitinib
- Glucosamine
- Griseofulvin
- Ifosfamide
- Itraconazole
- Ketoconazole
- Ketorolac
- Levamisole
- Mercaptopurine
- Methylphenidate
- Metronidazole
- Miconazole
- Mitotane
- NSAIDs
- Nalidixic Acid
- Neomycin
- Nevirapine
- Norfloxacin
- Ofloxacin
- Omeprazole
- Phenobarbital
- Phenytoin
- Propafenone
- Rifamycins
- Ritonavir
- Rivaroxaban
- Rosuvastatin
- Sorafenib
- St John's Wort
- Sucralfate
- Sulfinpyrazone
- Sulfonamides
- Sulfonylureas
- Tamoxifen
- Telaprevir
- Testolactone
- Testosterone
- Tetracyclines
- Thyroid Hormones
- Toremifene
- Tramadol
- Vemurafenib
- Venlafaxine
- Vitamin E
- Vitamin K
(Phytomenadione)
- Voriconazole

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2. British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin – fourth edition. Br J Haematol 2011; 154: 311–324
3. NPSA Actions that can make anticoagulant therapy safer (Mar 2007)
4. CKS. Oral anticoagulation – updated May 2013
5. HAS-BLED score for bleeding risk on oral anticoagulation in atrial fibrillation (AF). Accessed via:
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