

Drug Information Letter

No. 120

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Monitoring Drug Therapy

The aim of this bulletin is to provide information on the monitoring requirements for drugs in several therapeutic areas. The list of drugs is not exhaustive and information should be used in conjunction with any local policies already in place. This guidance does not address whether monitoring should be carried out within primary or secondary care. This issue should be discussed with general practitioners, primary care trusts and secondary care physicians.

Cardiovascular system (BNF Chapter 2)

| Drug | Suggested monitoring | Additional information |
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| Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-II receptor antagonists | <p>Baseline:</p> <ul style="list-style-type: none"> - BP, renal function and serum potassium¹ <p>Routine:</p> <ul style="list-style-type: none"> - BP, renal function and serum potassium 1 week after initiation, 1 week after each significant dose increase, and on an annual basis¹ | <p>Consider modifying/stopping treatment if:</p> <ul style="list-style-type: none"> - serum creatinine concentration increases by 50% or more² - serum potassium is 5.0 mmol/l or more |
| Diuretics (loop and thiazide) | <p>Baseline:</p> <ul style="list-style-type: none"> - serum potassium and urinalysis² <p>Routine:</p> <ul style="list-style-type: none"> - serum potassium 1 month after starting, and then after a change of dose or clinical circumstances² - urinalysis (glucose) should be performed annually² | <p>If serum potassium falls below 3.0mmol/l it may be necessary to add a potassium-sparing diuretic.</p> <p>Thiazides may induce diabetes mellitus.</p> |
| Amiodarone | <p>Baseline:</p> <ul style="list-style-type: none"> - LFTs, TFTs (T4, T3, TSH)³ - BNF recommends a chest x-ray,⁴ although not all clinicians consider this necessary - SPC recommends serum potassium and an ECG³ <p>Routine:</p> <ul style="list-style-type: none"> - TFTs should be checked every 6 months and continued for some months after discontinuation³ - LFTs should be checked every 6 months³ - annual ophthalmologic examination is recommended in the SPC³ although the need for this has been questioned. Patients frequently develop microdeposits in the cornea, however, these are considered essentially benign and do not require treatment. - if pulmonary toxicity is suspected during treatment, a chest x-ray should be carried out with lung function testing³ | <p>Measurement and interpretation of TFTs can be difficult in patients taking amiodarone. If hyperthyroidism develops, therapy should be discontinued.³ Hypothyroidism might warrant discontinuation of amiodarone, if clinically acceptable.</p> <p>Initial elevation of serum transaminases (1.5 to 3 times normal) may occur, which may return to normal with dose reduction, or sometimes spontaneously. Alteration of laboratory tests, which may be minimal (1.5 to 5 times normal), or clinical signs (e.g. hepatomegaly) during treatment greater than 6 months may indicate chronic liver disease, and should be investigated.³</p> |

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| Digoxin | Baseline: - serum creatinine ² Routine: - patients taking a diuretic should have their serum potassium monitored | Serum creatinine provides an estimate of renal function. Hypokalaemia may predispose the patient to digoxin toxicity. Regular monitoring of digoxin concentration is not necessary unless toxicity is suspected. |
| Warfarin | Baseline: - prothrombin time (PT) and activated partial thromboplastin time (APTT), platelet count and LFTs should be checked if possible, but this should not delay treatment ⁵ Routine: - once the patient's INR is within the therapeutic range, the INR should be monitored weekly until stable, and then at longer intervals (up to every 12 weeks) ⁵ | If there is any change in the patient's clinical condition (e.g. liver disease, illness, or drug administration) more frequent monitoring may be required. |
| Statins | Baseline: - serum cholesterol concentration ⁶ - LFTs ⁴ - CK Routine: - serum cholesterol should be checked annually ⁶ - CK should be checked within 1-3 months of starting treatment and thereafter whenever the cholesterol is measured. This is particularly important following an increase in statin dose and if statins are given with a fibrate or with ciclosporin (increased risk of rhabdomyolysis) - LFTs should be checked within 1-3 months of starting treatment and then at 6 months and 12 months, ⁴ unless indicated sooner by signs or symptoms of hepatotoxicity - manufacturers of atorvastatin and simvastatin make specific recommendations (see opposite) | Atorvastatin: After starting therapy, or after an increase in dose, LFTs should be repeated at 6 and 12 weeks, thereafter monitor every 6 months. ⁷ Simvastatin: LFTs should be checked twice a year for the first year of treatment or until 1 year after the last dose increase. Patients titrated to the 80mg dose should receive an additional test at 3 months. ⁸ Treatment should be discontinued if serum transaminase concentration rises to, and persists at, 3 times the upper limit of the reference range. Discontinue treatment if myopathy is suspected or diagnosed, and the CK is markedly elevated (>10 times upper limit of normal). |

Respiratory system (BNF Chapter 3)

| Drug | Suggested monitoring | Additional information |
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| Theophylline | Once a maintenance dose has been reached, serum theophylline concentration should be checked at 6-12 monthly intervals ⁹ | Theophylline has a narrow therapeutic index, and serum theophylline concentrations should be monitored to ensure they remain within the therapeutic range (10-20mg/l). Smoking increases the clearance of theophylline. |

Central nervous system (BNF Chapter 4)

Anti-epileptics

| Drug | Suggested monitoring | Additional information |
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| Carbamazepine | Baseline: - LFTs, FBC including platelets ¹⁰ Routine: - FBC should be performed periodically ¹⁰ (6-monthly ¹¹) - frequent monitoring of serum concentrations is not required, except when using other drugs that may interact and affect its metabolism, or when toxicity is suspected ¹¹ | Closely monitor the patient and the FBC if the WBC or platelet count is definitely low or decreases during therapy. Discontinue carbamazepine if any evidence of significant bone marrow depression appears, or the patient develops leucopenia. Withdraw carbamazepine in cases of aggravated liver dysfunction or acute liver disease. Raised GGT and AP is not an indication for withdrawal of the drug. The levels may be raised due to hepatic enzyme induction. |

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| Oxcarbazepine | <p>Baseline:</p> <ul style="list-style-type: none"> - patients with pre-existing renal conditions associated with low sodium or patients receiving sodium-lowering drugs as well as NSAIDs, should have serum sodium concentrations measured prior to initiating therapy¹² <p>Routine:</p> <ul style="list-style-type: none"> - the above patients should have serum sodium concentrations measured after 2 weeks, and then at monthly intervals for the first 3 months¹² | <p>Oxcarbazepine is a derivative of carbamazepine, however, the manufacturers do not recommend any of the monitoring described for carbamazepine.</p> <p>Oxcarbazepine induces hepatic enzymes to a lesser extent than carbamazepine. The BNF suggests that patients should be told how to recognise signs of blood, liver or skin disorders.⁴ Monitoring of serum concentrations is not indicated.</p> |
| Lamotrigine Levetiracetam Topiramate | No specific monitoring recommended | |
| Phenytoin | <p>Baseline:</p> <ul style="list-style-type: none"> - LFTs and FBC¹³ <p>Routine:</p> <ul style="list-style-type: none"> - FBC and LFTs regularly¹³ - folic acid levels every 6 months¹⁴ - serum phenytoin concentrations may be necessary for optimal dosage adjustments - the clinically effective level is usually 40-80mmol/l | <p>A period of 7 to 10 days is required to achieve steady state serum concentrations and changes in dosage should not be carried out at shorter intervals.</p> <p>Blood dyscrasias have occasionally been reported.</p> <p>Phenytoin may cause raised serum concentrations of AP and GGT and lowered serum concentrations of calcium and folic acid. Folic acid supplements should be given if necessary.</p> |
| Sodium valproate | <p>Baseline:</p> <ul style="list-style-type: none"> - LFTs - Bleeding time and coagulation tests to ensure there is no potential for bleeding complications¹⁵ <p>Routine:</p> <ul style="list-style-type: none"> - LFTs should be checked at monthly intervals during the first 3 months, and then annually¹³ | <p>Sodium valproate can cause thrombocytopenia. Spontaneous bruising or bleeding is an indication for withdrawal of the drug pending investigations.¹⁵</p> <p>Sodium valproate can cause hepatotoxicity. Modest rises in liver enzymes are usually insignificant and most problems occur in the first 12 weeks of therapy.</p> <p>Monitoring of serum concentrations is not indicated.</p> |
| Vigabatrin | <p>Baseline:</p> <ul style="list-style-type: none"> - visual field testing by perimetry¹⁶ <p>Routine:</p> <ul style="list-style-type: none"> - visual field testing by perimetry every 6 months¹⁶ | <p>Visual field defects have been reported in approximately one third of patients receiving vigabatrin.</p> <p>Monitoring of serum concentrations is not indicated.</p> |

Antipsychotic and antimanic drugs

| Drug | Suggested monitoring | Additional information |
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| Atypical antipsychotics (amisulpiride, olanzapine, quetiapine, risperidone, zotepine) | <p>Baseline:¹⁷</p> <ul style="list-style-type: none"> - CK, FBC, U&Es, LFTs, TFTs, BP, weight - prolactin concentrations should be checked in patients taking amisulpiride, olanzapine, risperidone and zotepine - blood glucose should be checked in patients taking olanzapine, quetiapine and zotepine - patients at risk of arrhythmias should have an ECG prior to starting zotepine <p>Routine:¹⁷</p> <p>Amisulpiride</p> <ul style="list-style-type: none"> - monitor FBC and U&Es every 6 months <p>Olanzapine</p> <ul style="list-style-type: none"> - check blood glucose every 3-6 months, FBC every 3-6 months, LFTs monthly for 3 months, U&Es every 6 months | <p>The SPCs for the atypical antipsychotics covered in this section contain very little guidance on monitoring requirements. The information in this section is based on the Maudsley Prescribing Guidelines.¹⁷</p> <p>Raised CK (>1000iu/L) may indicate possible neuroleptic malignant syndrome.¹⁷</p> <p>Stop medication and refer to haematologist if neutrophils fall below $1.5 \times 10^9/L$, risk of neutropenia.</p> |

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| | <p>Quetiapine</p> <ul style="list-style-type: none"> - check blood glucose every 3-6 months, FBC every 3-6 months, LFTs monthly for 3 months, TFTs every 6 months, and U&Es every 6 months <p>Risperidone</p> <ul style="list-style-type: none"> - FBC and LFTs should be checked every 3-6 months, U&Es every 6 months <p>Zotepine</p> <ul style="list-style-type: none"> - check blood glucose every 3-6 months, ECG when maintenance dose reached, FBC every 3-6 months, LFTs every 3-6 months, U&Es every 6 months | <p>Patients with hepatic impairment taking zotepine should have their LFTs monitored weekly for the first 3 months.</p> |
| Clozapine | <p>Baseline:</p> <ul style="list-style-type: none"> - patients must have a WBC count $>3.5 \times 10^9/L$ and a normal differential blood count¹⁸ - blood glucose, BP, CK, ECG, EEG, LFTs, U&Es, weight¹⁷ <p>Routine:</p> <ul style="list-style-type: none"> - WBC count and differential count must be monitored weekly for the first 18 weeks and then at least at 2 week intervals for the first year of therapy. After the patient has been on treatment for 1 year with stable neutrophil counts over that period, then the frequency of monitoring may be changed to 4 week intervals. - CPMS monitoring should be supplemented with 3-6 monthly checks of patients' LFTs, U&Es, ECG and blood glucose^{11,17} | <p>The use of clozapine is restricted to patients who are registered with the Clozaril Patient Monitoring Service (CPMS).</p> <p>Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of clozapine.¹⁸</p> <p>Patients with pre-existing liver disorders may receive clozapine but need regular LFT monitoring.</p> |
| Lithium | <p>Baseline:</p> <ul style="list-style-type: none"> - TFTs, renal and cardiac function¹¹ <p>Routine:</p> <ul style="list-style-type: none"> - serum lithium concentrations must be checked weekly until the patient is stabilised, and then monitored regularly, at least every 3 months - TFTs should be checked every 3-6 months in women, annually in men¹¹ - renal function should be checked at monthly intervals for 3 months, and then every 3 months | <p>Lithium is contra-indicated in patients with cardiac disease.</p> <p>Blood should be taken for serum lithium concentrations at least 12 hours after the last dose. It is normal practice to aim for concentrations between 0.4 and 0.8mmol/l. Lithium concentrations should be monitored if the patient becomes dehydrated or has diarrhoea or vomiting.</p> <p>24-hour creatinine clearance tests should be performed annually in patients who have been on lithium for more than 5 years, or show changes in standard renal function tests.¹¹</p> |

Infections (BNF Chapter 5)

| Drug | Suggested monitoring | Additional information |
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| Minocycline | <p>If minocycline is continued for longer than 6 months, monitor the patient every 3 months for signs and symptoms of hepatotoxicity, systemic lupus erythematosus (SLE), or unusual pigmentation¹⁹</p> | <p>Discontinue minocycline if the patient develops signs or symptoms of hepatotoxicity, SLE or unusual pigmentation.</p> |

Endocrine system (BNF Chapter 6)

| Drug | Suggested monitoring | Additional information |
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| Thyroxine | <p>Baseline:</p> <ul style="list-style-type: none"> - TSH and T4 <p>Routine:</p> <ul style="list-style-type: none"> - TSH levels should be measured following a change in dose (3 - monthly is common practice) then yearly once the condition is stable²⁰ | <p>A pre-therapy ECG may be of value as changes induced by hypothyroidism may be confused with evidence of ischaemia.⁴</p> |

Musculoskeletal and joint diseases (BNF Chapter 10)

| Drug | Suggested monitoring | Additional information |
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| Azathioprine | <p>Baseline:</p> <ul style="list-style-type: none"> - FBC, U&Es, creatinine and LFTs²¹ <p>Routine:</p> <ul style="list-style-type: none"> - FBC weekly for the first 8 weeks of therapy,²² 2 and 4 weeks after each dose increase,²¹ and then monthly - LFTs monthly until the dose is stable | <p>NB The BNF advises weekly monitoring of FBC for the first 4 weeks only, and questions the practical value of weekly monitoring for the first 8 weeks.⁴</p> <p>If any of the following results are received, treatment should be withheld until discussed with rheumatologist:²¹</p> <ul style="list-style-type: none"> - WBC $<4.0 \times 10^9/l$ - neutrophils $<2.0 \times 10^9/l$ - platelets $<150 \times 10^9/l$ - >2-fold rise in AST, ALT, or AP (from upper limit of reference range) |
| Hydroxychloroquine | <p>Baseline:</p> <ul style="list-style-type: none"> - LFTs and renal function²³ - record near visual acuity of each eye (with glasses where appropriate) using a reading chart²³ <p>Routine:</p> <ul style="list-style-type: none"> - visual acuity should be checked at least every 12 months²⁴ - periodic blood counts should be performed to check for bone marrow depression²⁴ | <p>The SPC states that the ophthalmologic examination should include testing visual acuity, careful ophthalmoscopy and central visual field testing with a red target.²⁴</p> <p>Due to the complex nature of this monitoring, it may be advisable to liaise with local ophthalmologists to negotiate a screening protocol.</p> |
| Leflunomide | <p>Baseline:</p> <ul style="list-style-type: none"> - FBC including differential WBC count and platelets, ALT and AST^{21,25} <p>Routine:</p> <ul style="list-style-type: none"> - ALT and BP must be checked monthly or at more frequent intervals during the first 6 months and every 8 weeks thereafter - FBC including differential WBC count and platelets should be performed every 2 weeks for the first 6 months and then every 8 weeks^{21,25} | <p>If any of the following results are received, treatment should be withheld until discussed with rheumatologist:²¹</p> <ul style="list-style-type: none"> - WBC $<4 \times 10^9/l$ - neutrophils $<2 \times 10^9/l$ - platelets $<150 \times 10^9/l$ - >2-fold rise in ALT or AST (from upper limit of reference range) |
| Methotrexate | <p>Baseline:</p> <ul style="list-style-type: none"> - renal function, LFTs, FBC and chest x-ray²⁶ <p>Routine:</p> <ul style="list-style-type: none"> - FBC should be checked weekly until 6 weeks after the last dose increase, then monthly²¹ - LFTs (including AST or ALT) should be checked monthly and U&Es 6-12 monthly²¹ <p>NB manufacturer's advice differs (see opposite)</p> | <p>SPC suggests that FBC, urinalysis, renal function tests, and LFTs are performed every 2-3 months.²⁶ This monitoring would also apply to patients receiving methotrexate for the treatment of psoriasis.</p> <p>If any of the following results are received, treatment should be withheld until discussed with relevant clinician²¹</p> <ul style="list-style-type: none"> - WBC $<4.0 \times 10^9/l$ - neutrophils $<2.0 \times 10^9/l$ - platelets $<150 \times 10^9/l$ - >2-fold rise in ALT or AST (from upper limit of reference range) - unexplained fall in albumin |
| Penicillamine | <p>Baseline:</p> <ul style="list-style-type: none"> - FBC and platelet counts, plus renal function (urinalysis, U&Es, creatinine)²⁷ <p>Routine:</p> <ul style="list-style-type: none"> - urinalysis and FBC should be checked fortnightly until on a stable dose²¹ | <p>If any of the following results are received, treatment should be withheld until discussed with rheumatologist:²¹</p> <ul style="list-style-type: none"> - WBC $<4.0 \times 10^9/l$ - neutrophils $<2.0 \times 10^9/l$ - platelets $<150 \times 10^9/l$ - $>++$ proteinuria on more than 1 occasion - $>++$ haematuria on more than 1 occasion |
| Sodium aurothiomalate | <p>Baseline:</p> <ul style="list-style-type: none"> - FBC, urinalysis, U&Es, serum creatinine and LFTs²⁸ <p>Routine:</p> <ul style="list-style-type: none"> - before each injection, FBC and urinalysis should be obtained | <p>It is permissible to work one FBC in arrears.²¹</p> <p>If any of the following laboratory test results are received, treatment should be withheld until discussed with rheumatologist:²¹</p> <ul style="list-style-type: none"> - WBC $<4.0 \times 10^9/l$ - neutrophils $<2.0 \times 10^9/l$ - platelets $<150 \times 10^9/l$ - $>++$ proteinuria on more than 1 occasion |

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| Sulphasalazine | <p>Baseline:</p> <ul style="list-style-type: none"> - FBC (differential white cell, red cell and platelet counts), LFTs and renal function^{21,29} <p>Routine:</p> <ul style="list-style-type: none"> - FBC should be checked fortnightly for the first 12 weeks, and then 12 weekly thereafter²¹ - LFTs (including ALT or AST) should be checked every 4 weeks for the first 12 weeks, and then 12 weekly²¹ - The SPC advises that renal function should be checked at regular intervals,²⁹ although the BNF questions the value of such regular monitoring⁴ | <p>If during the first year of treatment blood results have been stable, 6 monthly tests can be performed for the second year and, thereafter, monitoring of blood for toxicity can be discarded.²¹</p> <p>If any of the following results are received, treatment should be withheld until discussed with rheumatologist:²¹</p> <ul style="list-style-type: none"> - WBC <4.0x10⁹/l - neutrophils <2.0x10⁹/l - platelets <150x10⁹/l - >2-fold rise in ALT or AST (from upper limit of reference range) |
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Abbreviations

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| ALT | alanine aminotransferase | FBC | full blood count |
| AP | alkaline phosphatase | GGT | gamma glutamyl transpeptidase |
| AST | aspartate aminotransferase | LFTs | liver function tests |
| BNF | British National Formulary | SPC | Summary of Product Characteristics |
| BP | blood pressure | TFTs | thyroid function tests |
| CK | creatinase kinase | T4 | thyroxine |
| CPMS | Clozaril Patient Monitoring Service | TSH | thyroid-stimulating hormone |
| ECG | echocardiogram | U&Es | urea and electrolytes |
| EEG | electroencephalogram | WBC | white blood cell |

References

- 1 Eccles M et al. North of England evidence based development project: guideline for angiotensin converting enzyme inhibitors in primary care management of adults with symptomatic heart failure. *BMJ* 1998;**316**:1369-75
- 2 Hippisley-Cox J et al. Monitoring requirements for cardiovascular drugs. *Prescriber* 2000;**11**(2):43-56
- 3 Codarone X. Summary of product characteristics November 2001. Sanofi Synthelabo
- 4 British National Formulary. 43rd edition March 2002. Pub: BMA & RPSGB
- 5 Haemostasis and Thrombosis task force. Guidelines on oral anticoagulation: third edition. *Br J Haematol* 1998;**101**:374-87
- 6 National Institute for Clinical Excellence. Inherited clinical guideline A. Prophylaxis for patients who have experienced a myocardial infarction. April 2000
- 7 Lipitor. Summary of product characteristics May 2000. Parke Davis
- 8 Zocor. Summary of product characteristics March 2000. Merck Sharp & Dohme
- 9 Martindale. The complete drug reference 33rd edition. Pub: Pharmaceutical Press, 2002
- 10 Tegretol. Summary of product characteristics June 2001. Cephalon UK Ltd
- 11 Blacker R. Monitoring requirements necessary with CNS drugs. *Prescriber* 1999;**10**(18):63-71
- 12 Trileptal. Summary of product characteristics May 2002. Novartis Pharmaceuticals UK Ltd
- 13 Crawford P. Monitoring requirements with antiepileptic drugs. *Prescriber* 1999;**10**(22):122-23
- 14 Epanutin. Summary of product characteristics June 2000. Parke Davis
- 15 Epilim. Summary of product characteristics March 2001. Sanofi Synthelabo
- 16 Sabril. Summary of product characteristics December 2001. Aventis Pharma Ltd
- 17 Taylor D et al. The Maudsley 2001 Prescribing Guidelines 6th edition. Martin Dunitz Ltd
- 18 Clozaril. Summary of product characteristics May 2002. Novartis Pharmaceuticals UK Ltd
- 19 Minocin MR. Summary of product characteristics July 1999. Wyeth Laboratories
- 20 Personal communication Dr E Manning, Department of Clinical Chemistry, Royal Liverpool University Hospital. August 2002
- 21 The British Society of Rheumatology. Guidelines for second line drug monitoring. 2nd edition July 2000
- 22 Imuran. Summary of product characteristics April 1999. GlaxoSmithKline UK
- 23 The Royal College of Ophthalmologists. Ocular toxicity and hydroxychloroquine. Guidelines for screening 1998
- 24 Plaquenil. Summary of product characteristics August 2000. Sanofi Synthelabo
- 25 Arava. Summary of product characteristics March 2002. Aventis Pharma Ltd
- 26 Methotrexate sodium tablets. Summary of product characteristics May 2000. Wyeth Laboratories
- 27 Distamine. Summary of product characteristics May 2000. Dista Products Ltd
- 28 Myocrisin. Summary of product characteristics November 1999. JHC Healthcare Ltd
- 29 Salazopyrin. Summary of product characteristics July 2001. Pharmacia