*Somerset Healthcare Community Shared Care Protocol for the use of **Lithium***

This shared care protocol (SCP) sets out details for the sharing of care in monitoring and management of patients who are prescribed lithium within its licensed indications. It should be read in conjunction with the Summary of Products Characteristics (SPC, available at [www.emc.medicines.org.uk)](www.emc.medicines.org.uk)

As outlined in NHS Circular 1992 (Gen 11), when a consultant considers a patients' condition is stable he/she may seek the agreement of the patients' GP to "share" the patients' care. This document provides information on drug treatment for the shared commitment between the consultant and GP concerned. GPs are invited to participate. If the GP is not confident to undertake these roles, then they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

Introduction

This shared care guideline sets out details to support the transfer of responsibility for prescribing lithium from secondary to primary care.
It is intended to apply to patients who have been initiated on treatment, (and who have been assessed as benefiting) by secondary care services experienced in the care of people with mental health issues in accordance with the guidance from the National Institute for Health & Clinical Excellence for the following licenced indications:

- Prophylaxis of bipolar affective disorder.
- Treatment of acute manic or hypomanic episodes.
- Treatment of episodes of recurrent depressive disorders where treatment with other antidepressants has been unsuccessful.

The margin between the therapeutic and the toxic concentration of lithium is narrow. Safe and effective use of lithium requires regular monitoring of plasma lithium concentration and careful monitoring of renal and thyroid function.

Lithium treatment will usually be initiated in secondary care. A clear diagnosis and reason for lithium prophylaxis, together with an indication of the desired plasma lithium concentration and any reasons for cautions in treatment (e.g. renal impairment or concurrent medication) should be recorded.

Recommendations for prescribing and monitoring lithium and safe management of patients are included in the NPSA and NICE publications below:

- NPSA Patient Safety Alert 'Safer Lithium Therapy' (December 2009)- http://www.nrls.npsa.nhs.uk/alerts/?entryid45=65426
- NICE Clinical Guideline 38 – Bipolar disorder (July 2006)- https://www.nice.org.uk/guidance/CG38
- NICE Clinical Guideline 90 – Depression (October 2009)- https://www.nice.org.uk/Guidance/CG90

Drug treatment should form part of a wider package of support and information for the patient and their carer.

For further information please click on the links below or visit;

British National Formulary

https://www.evidence.nhs.uk/formulary/bnf/current/4-central-nervous-system/42-drugs-used-in-psychoses-and-related-disorders/423-drugs-used-for-mania-and-hypomania/lithium

http://www.medicines.org.uk/emc/

Dose (posology & method of administration): see individual SPCs at http://www.medicines.org.uk/emc/

Please refer to the individual manufacturers' summaries of product characteristics for full prescribing information on dose, including dose in impaired renal function. Only licensed doses should be used.

- The consultant should indicate the current dose and target plasma lithium concentration for each patient. The dose should be adjusted so as to achieve the desired therapeutic range. The minimum clinically effective dose of lithium should always be used.
- Due to variations in pharmacokinetics and bioavailability a patient should always receive the same brand and formulation of lithium (unless there is a clinical reason to change it) and this should be indicated on the prescription, patient monitoring booklet and in all relevant documentation and correspondence.
- Lithium should normally be taken as a single night time dose of a modified release preparation, preferably in the evening to facilitate monitoring of steady state plasma lithium concentration 12 hours post-dose. Liquid preparations need to be taken twice a day.

Contraindications

- Hypersensitivity to lithium or to any of the excipients
- Cardiac disease
- Cardiac insufficiency
- Severe renal impairment
- Untreated hypothyroidism
- Breastfeeding
- Patients with low body sodium levels, or those on low sodium diets
- Patient who are dehydrated
- Addison's disease
- Children under 18 years
- Brugada syndrome or family history of Brugada syndrome

Special warnings and precautions

Before beginning lithium treatment

- Renal function should be assessed and lithium avoided in patients with severe renal impairment.
- Cardiac function should be assessed and lithium avoided in patients with cardiac insufficiency.
- Thyroid function should be evaluated. Patients should be euthyroid before initiation of therapy.

- An ECG should be carried out; lithium should be used with caution in patients with risk factors such as QT interval prolongation (e.g. uncorrected hypokalaemia or bradycardia), and in patients concomitantly treated with drugs that are known to prolong the QT interval
- Particular care should be taken in women of child bearing age, and avoid if possible in the first trimester due to the risk of teratogenicity, including cardiac abnormalities.
- Special care should be used in the elderly, as this age group may be particularly susceptible to toxicity due to decreasing renal function.

Patients should be informed of:

- Symptoms of lithium toxicity and they should be advised to stop treatment and seek medical advice immediately if symptoms of toxicity appear.
- Symptoms of polyuria or polydipsia develops and to seek medical advice if symptoms occur.
- The potential for drug interactions including over the counter medicines.
- The need to seek medical advice if any episodes of nausea, vomiting, diarrhoea, excessive sweating, and/or other conditions leading to salt/water depletion (including infection or severe dieting) occur.
- The need to maintain an adequate fluid intake and constant salt intake in order to maintain a stable electrolyte balance. This may be of special importance in very hot weather or work environment.

Patients should be given the NPSA Lithium Therapy pack (see below) and an entry made in their record that written and verbal information regarding lithium therapy has been provided.

NPSA Patient Safety Alert Safer lithium therapy (December 2009). The NPSA has developed a patient information booklet, lithium alert card and record book for tracking blood tests and to support communication between healthcare providers and empower patients. Blood test results should be checked before prescribing or dispensing lithium, although as a principle therapy should not be withheld due to the high risk of relapse, but the relevant parties should be informed.

During lithium treatment

- Renal, cardiac and thyroid function should be monitored regularly.
- Plasma lithium concentration should be monitored regularly.
- In the treatment of bipolar disorder NICE guidance suggests a target range of 0.6-0.8mmol/L unless the patient has relapsed previously on lithium, has sub-syndromal symptoms or has acute mania, in which case a higher level may be appropriate.
- Blood samples should be taken 12 hours post dose for plasma lithium concentration measurement every week until the dose has remained constant for 4 weeks and the plasma lithium concentration has stabilised within the target range. Lithium levels should then be checked every 3 months unless more frequent monitoring is indicated (see monitoring section).

Drug interactions (see the latest BNF or Summary of Product Characteristics (SPC) at www.medicines.org.uk/emc/ for a full list of possible drug interactions)

Interacting medication can be very dangerous for the patient and should be avoided where at all possible. Where appropriate, either lithium dosage should be adjusted or concomitant treatment changed. The following list is not exhaustive but highlights a few of the potential drug interactions:

- **Drugs that prolong the QT interval + Other drugs that prolong the QT interval** - concurrent use of more than one drug that prolongs the QT interval increases the risk of torsade de pointes, which may lead to life-threatening ventricular arrhythmias. The risk varies with different combinations of drugs that prolong the QT interval, and with the presence of other risk factors for this effect.
- **Sodium** - ingestion of marked amounts of sodium (for example in over the counter antacid preparations) may prevent the establishment or maintenance of an adequate plasma lithium concentration. Conversely, dietary salt restriction can cause the plasma lithium concentration to rise to toxic levels if the lithium dose is not reduced appropriately.
- **Thiazide diuretics** - may increase the plasma lithium concentration markedly by reduced renal lithium excretion. This may occur quickly (over days). If the combination is unavoidable very close monitoring of plasma lithium concentration and for signs of lithium toxicity is required, especially when treatment is initiated or changed. The elderly are especially susceptible.
- **Loop diuretics** in combination with lithium are generally considered to be safer than thiazide diuretics although isolated cases of toxicity have been reported. Close monitoring of plasma lithium concentration and for signs of lithium toxicity is required, especially when treatment is initiated or changed.
- **NSAIDs** - increase the plasma lithium concentration by reducing renal lithium excretion. If the combination is unavoidable **very** close monitoring of plasma lithium concentration and for signs of lithium toxicity is required, especially when treatment is initiated or changed.
- **ACE inhibitors and angiotensin II receptor antagonists** - increase the plasma lithium concentration by reducing renal lithium excretion and they can also precipitate renal failure. If the combination is unavoidable **very** close monitoring of plasma lithium concentration and for signs of lithium toxicity is required, especially when treatment is initiated or changed.
- **Amiodarone –** risk of ventricular arrhythmias.
- **Antipsychotics –** increased risk of extrapyramidal side-effects and possible neurotoxicity.
- **Carbamazepine and phenytoin –** possible neurotoxicity, carbamazepine can cause hyponatraemia and neurotoxicity without an increase in lithium plasma concentration**.**
- **Clonazepam –** Possible neurotoxicity and increased lithium levels.
- **Methyldopa** - risk of neurotoxicity without increased plasma lithium concentration**.**
- **Venlafaxine –** risk of serotonin syndrome.
- **SSRIs –** risk of serotonin syndrome and fluoxetine may alter the plasma lithium concentration. SSRI's can cause hyponatraemia**.** The combined use of citalopram or escitalopram with other drugs that prolong the QT interval, such as lithium, is contraindicated. If the combination is unavoidable, the current advice is to monitor ECG at baseline and every 6 months.
- **Other possible interactions:** baclofen, diltiazem, metronidazole, tetracyclines, potassium-sparing diuretics and aldosterone antagonists, sumatriptan, theophylline, verapamil, corticosteroids. See product literature for full details.

Pregnancy and lactation: (See SPCs at http://www.medicines.org.uk/emc/)

Pregnancy

Lithium therapy should not be used during pregnancy, especially during the first trimester- consult specialist advice

Lactation

Lithium is present in breast milk and a decision to discontinue lithium therapy or discontinue breastfeeding the child needs to be made.

Adverse effects: (see the latest BNF or Summary of Product Characteristics (SPC) at www.medicines.org.uk/emc/ for a full list of possible adverse effects).

Adverse effects to lithium are usually related to plasma lithium concentration and are less common when levels are below 1.0mmol/L. Mild gastrointestinal effects such as nausea, a general discomfort and vertigo, may occur initially, but frequently disappear after the first few days of lithium administration. Fine hand tremors, polyuria and mild thirst may persist.

- **Blood and lymphatic system disorders** - Leucocytosis
- **Endocrine disorders** - Long-term adverse effects may include thyroid function disturbances such as euthyroid goitre and/or hypothyroidism and thyrotoxicosis. Lithium-induced hypothyroidism may be managed successfully with concurrent thyroxine. Hypercalcaemia, hypermagnesemia, hyperparathyroidism have been reported.
- **Metabolism and nutrition disorders** - Weight increase, hyperglycaemia
- **Psychiatric disorders** – Confusion, delirium
- **Nervous system disorders** - Ataxia, hyperactive deep tendon reflexes, slurred speech, dizziness, nystagmus, stupor, coma, myasthenia gravis, giddiness, dazed feeling, memory impairment. Tremor, especially fine hand tremors, vertigo, dysarthria, impaired consciousness, myoclonus, abnormal reflexes, convulsions, benign intracranial hypertension, extrapyramidal disorders.
- **Cardiac disorders** - Cardiac arrhythmia, mainly bradycardia, sinus node dysfunction, peripheral circulatory collapse, hypotension, ECG changes such as reversible flattening or inversion of T-waves and QT prolongation, AV block, cardiomyopathy.
- **Gastrointestinal disorders** - Abdominal discomfort, taste disorder, nausea, vomiting, diarrhoea, salivary hypersecretion, dry mouth, anorexia. Mild gastrointestinal effects may occur initially, but frequently disappear after the first few days of lithium administration
- **Skin and subcutaneous tissue disorders** - Folliculitis, pruritus, papular skin disorders, acne or acneform eruptions, aggravation or occurrence of psoriasis, allergic rashes, alopecia, cutaneous ulcers.
- **Musculoskeletal and connective tissue disorders** - Muscle weakness
- **Renal and urinary disorders** - Polydipsia and/or polyuria and nephrogenic diabetes insipidus, histological renal changes with interstitial fibrosis after long term treatment have been reported. This is usually reversible on lithium withdrawal. Long-term treatment with lithium may result in permanent changes in kidney histology and impairment of renal function. High plasma concentrations of lithium including episodes of acute lithium toxicity may aggravate these changes. Rare cases of nephrotic syndrome have been reported.
- **General disorders** - Peripheral oedema
- **Reproductive system** - Sexual dysfunction
- **Senses** - Dysgeusia, blurred vision and scotomata

Lithium toxicity

Whenever a patient on lithium presents feeling unwell or displaying any of the above symptoms, the possibility of lithium toxicity should be considered. Plasma lithium concentration should be checked and the patient medically reviewed. If serious adverse effects are suspected treatment should be stopped until the plasma lithium concentration has been checked.

Factors which increase the risk of lithium toxicity, include renal impairment, reduced sodium intake, increased sodium loss or changes in fluid balance (e.g. diarrhoea, vomiting, infection, hot weather, sweating, severe dieting,), diuretics, NSAIDs and other interacting drugs (see drug interactions).

Signs of lithium toxicity include: increasing diarrhoea, vomiting, anorexia, muscle weakness, lethargy, giddiness with ataxia, lack of coordination, tinnitus, blurred vision, coarse tremor of the extremities and lower jaw, muscle hyperirritability, choreoathetoid movements, dysarthria, and drowsiness.

Symptoms of severe overdosage at plasma lithium concentrations above 2mmol/L include: hyperreflexia and hyperextension of limbs, syncope, toxic psychosis, seizures, polyuria, renal failure, electrolyte imbalance, dehydration, circulatory failure, coma, and death.

Products and costs: (BNF No. 63, March 2012)

Because of variations in pharmacokinetics and bioavailability a patient should always receive the same lithium preparation (unless there is a clinical reason to change it) and **this should be indicated on the prescription**, patient held record book and in all relevant documentation and correspondence.

Drug	Strength	Pack size	Cost per pack
Priadel® Tablets	200mg (Li^+ 5.4mmol)	100 tablets	£2.76
(Lithium Carbonate)	400mg (Li^+ 10.8mmol)	100 tablets	£4.02
Camcolit® Tablets	250mg (Li^+ 6.8mmol)	100 tablets	£48.18
(Lithium Carbonate)	400mg (Li^+ 10.8mmol)	100 tablets	£48.18
Liskonium® Tablets (Lithium Carbonate)	450mg (Li^+ 12.2mmol)	60 tablets	£2.88
Priadel® Liquid (Lithium Citrate)	520mg/5ml (Li^+ 5.4mmol/5ml)	150ml	£6.73
Li-Liquid®	509mg/5ml (Li^+ 5.4mmol/5ml)	150ml	£5.79
(Lithium Citrate)	1.018 g/5 ml (Li^+ 10.8 mmol/5 ml)	150ml	£11.58

The Summaries of Product Characteristics (SmPCs) at www.medicines.org.uk/emc/ should be consulted for full information

Shared Care Responsibilities

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to, and accepted by, the patient. This provides an opportunity to discuss drug therapy.

The clinician who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

Secondary Care responsibilities

- Diagnosis of mania, hypomania, bipolar disorder or recurrent depression following full assessment.
- Arrange a pre-treatment assessment including general health screen and check of renal, thyroid and cardiac status (including ECG. The tests themselves can be undertaken in primary care or secondary care but interpretation of results and clinical responsibility will remain with secondary care.
- Educate the patient about lithium therapy including how to recognize the signs of toxicity.
- Provide the patient with the NPSA patient booklet, alert card and record book.
- To initiate therapy and prescribe lithium until the dose has remained constant and the plasma lithium concentration stabilised within the desired range.
- Arrange transfer of prescribing and monitoring to the patient's GP when a maintenance dose has been determined and provide GP with a personalised copy of this shared care protocol.
- Provide the GP with appropriate information to include monitoring arrangements, target plasma lithium concentration and length of treatment, to support the transfer of clinical responsibility.
- Inform the patient/carer of arrangements for further prescriptions and monitoring.
- Notify the GP of the results of patient reviews including any changes in prescribed therapy.
- Document test results and any changes in the patient held record book.

General Practitioner responsibilities

- Refer patients to secondary care raising possibility of mania, hypomania, bipolar disorder or recurrent depression.
- Accept request to take on prescribing of lithium once the consultant considers a patient's condition is stable and the patient is on a tolerated dose effective for symptom control.
- Reinforce educational points provided by secondary care.
- Carry out on-going monitoring as outlined below and review blood test results before repeat prescribing.
- Document test results and any changes in the patient held record book.
- Perform the annual review if the patient is discharged from the psychiatric service.
- Inform the consultant of any changes in the patient's medical condition and/or prescribed medication, especially adverse effects.
- Make urgent arrangements for re-referral in the event of relapse or pronounced change in mental state or suspected non-adherence to medication.
- Stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises and refer back to secondary care.
- Ensure female patients of child bearing age are using effective contraceptive methods
- Refer to specialist if pregnancy occurs

Monitoring
Blood should be taken for the following investigations, observing all due safety precautions if there is a risk of blood-borne infection:

- **Plasma lithium concentration** - at least every 3 months once stable
- **U&Es/creatinine/eGFR** - at least every 6 months; every 3 months recommended
- **Calcium** - at least every 6 months
- **TFTs** - TSH every 6 months
  - every 3 months if abnormal or on thyroid supplements
- **Others e.g.** - FBC, ECG, calcium, pregnancy test – as clinically indicated
- **Weight and blood pressure** - at annual review

Blood samples for lithium levels should be taken in the morning to enable measurement of twelve hour post-dose levels. Patients on lithium tablets should be advised to take their dose in the evening; patients on twice daily liquid preparations should delay their morning dose until after the blood test.

Additional plasma lithium concentration monitoring will be needed in the following cases:

- Change of dose, brand or formulation
- In the elderly
- In those with renal impairment
- Concurrent medications with potential for interactions e.g. NSAIDs, ACE inhibitors, diuretics (see drug interactions section)
- Signs of manic or depressive relapse
- Changes in sodium or fluid intake, including acute illness that may result in dehydration
- Suspected lithium toxicity or non-adherence
- Significant weight change

Length of treatment
The consultant psychiatrist will advise on duration of treatment.

Stopping lithium therapy
Except where there are signs of toxicity, this should be done gradually over at least a month (and preferably 3 months) to reduce the risk of relapse associated with abrupt discontinuation, following liaison with a consultant psychiatrist. Monitor any ongoing need for thyroid supplements. Additional advice should also be sought in the case of surgery or pregnancy.

Patient/ carer responsibilities

- To adhere to medication.
- To agree to regular blood tests and monitoring.
- To maintain regular salt and water intake.
- To report any significant signs or symptoms relating to their condition, including side effects or concordance issues to the GP.

Further support

- Medicines Information department, Musgrove Park Hospital: 01823 342253
- Medicines Information department, Yeovil District Hospital: 01935 384327
- Prescribing & Medicines Management Team, NHS Somerset: 01935 384123
- Medicines Management Team, Somerset Partnership: 01823 368265

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Drawn up by:	Margaret Davies, Chief Pharmacist, Somerset Partnership NHS Foundation Trust	July 2010
Reviewed by:	Anne Cole, Senior Clinical Pharmacist Somerset Partnership NHS Foundation Trust	Sep 2012
Reviewed by:	Catherine Henley and Sam Morris, Medicines Managers Somerset CCG Rosemary Brook, Consultant Psychiatrist, Somerset Partnership NHS Foundation Trust	June 2017
Approved by:	Somerset Prescribing Forum, NHS Somerset	
	Drug & Therapeutics Committee, Taunton & Somerset NHS FT	N/A
	Drug & Therapeutics Committee, East Somerset NHS FT	N/A
	Medicines in Clinical Practice Group, Somerset Partnership NHS FT	June 2017
Review required by:		June 2020

References:

- NPSA Patient Safety Alert Safer Lithium Therapy December 2009. http://www.nrls.npsa.nhs.uk/alerts/?entryid45=65426
- NICE Clinical Guideline CG185 – Bipolar disorder, Sept 2014 https://www.nice.org.uk/guidance/cg185
- NICE Clinical Guideline 90 – Depression October 2009. https://www.nice.org.uk/Guidance/CG90
- BNF online updated 28/04/2017. https://bnf.nice.org.uk/
- Summary of Product Characteristics for Priadel; Camcolit; Liskonium; Li-Liquid http://www.medicines.org.uk/emc/search#search/?q=lithium&dt=1&_suid=1496847692742000971845174402635 7
- Somerset Partnership NHS Foundation Trust Lithium Guidelines 2013 http://intranet.sompar.nhs.uk/system_pages/idoc.ashx?docid=9f2fe98b-d56d-40b0-8d1f-4143db8199c5&version=-1
- NICE Clinical Guideline182– Chronic kidney disease in adults, July 2014 https://www.nice.org.uk/guidance/cg182
- Lithium and eGFR: a new routinely available tool for the prevention of chronic kidney disease, Morriss & Benjamin, British Journal of Psychiatry 2008; 193: 93-95
- Lithium and chronic kidney disease, Kripalani et al, BMJ 2009: 339:b2452

Appendix 1

Somerset Partnership notes on interpreting tests of renal function

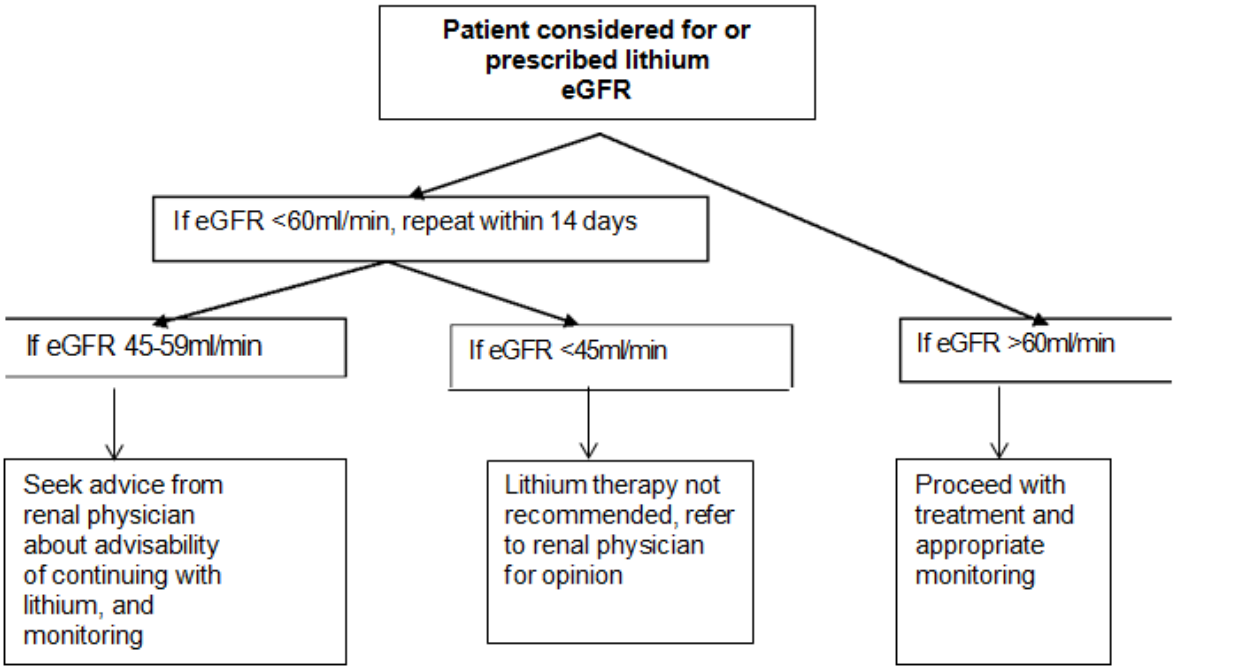
Whilst the eGFR is a useful tool it is only an estimate of renal function based on the Modification of Diet in Renal Disease (MDRD) formula, which assumes a body surface area of 1.73 m^2, and is not valid unless serum creatinine level is stable. It is inaccurate in:

- Under 18's
- malnourished/dehydrated
- Over 70's
- amputees
- Afro-Caribbean's
- eGFR >60 ml/min

It can also be affected by muscle injury, injections, or eating meat within 12 hours of the test as these will all influence creatinine levels. A 20% fall in eGFR for an individual reflects an important change.

Consider referring for specialist renal opinion:

- Rapidly falling eGFR >5 ml/min in 1 year or 10 ml/min in 5 years with progressive fall of eGFR on > 3 serial tests (especially important if eGFR is < 45ml/min)
- Progressive rise in serum creatinine level on > 3 serial tests e.g. 20% increase
- Fall in eGFR to below 45 ml/min
- eGFR < 60ml/min and unexplained anaemia (Hb <11g/dl), abnormal potassium,



Other evidence of chronic kidney disease is one or more of the following: persistent microalbuminuria, persistent proteinuria, persistent haematuria