Shared Care Guideline

Metolazone for fluid management in CKD (Adults)

It is vital for safe and appropriate patient care that there is a clear understanding of where clinical and prescribing responsibility rests between Consultants and General Practitioners (GPs).
This guideline reinforces the basic premise that:
When clinical and / or prescribing responsibility for a patient is transferred from hospital to GP, the GP should have full confidence to prescribe the necessary medicines. Therefore, it is essential that a transfer of care involving medicines that a GP would not normally be familiar with, should not take place without the "sharing of information with the individual GP and their mutual agreement to the transfer of care."
These are not rigid guidelines. On occasions, Consultants and GPs may agree to work outside of this guidance. As always, the doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

Indication:
Metolazone is approved for use in combination with a loop diuretic for management of CKD 4/5 by nephrologists.

This is a second line agent for the above indication for the few patients that do not respond sufficiently to loop diuretics alone, but have adequate urine output to warrant pursuing intensive diuresis with metolazone.

Dosage and administration:
Starting dose: 2.5mg on alternative days or daily.

Titrated by 2.5mg dose units according to response.

Maximum dose: 7.5mg daily.

Contraindications:

- Refractory hypokalaemia
- Hyponatraemia
- Hepatic impairment
- Symptomatic hyperuricaemia
- Anuria
- Symptomatic hypercalcaemia
- Addison's disease

Cautions:

- Diabetes and gout may be aggravated
- Hepatic impairment
- Pregnancy
- SLE
- Nephrotic Syndrome

Additional Information
Sanofi-Aventis discontinued the manufacturing of metolazone in 2012. Metolazone is now only available as an **unlicensed** special order item in the UK.

Metolazone can promote dramatic diuresis and disturbance in fluid balance and electrolytes. Patients must be closely monitored and specialist initiation & advice is required.
Treatment in the majority of patients will be short term & undertaken in secondary care inpatient setting only. There may however be a very small number of cases where maintenance therapy with metolazone needs to continue on discharge from the hospital, or it may need to be initiated in the community heart failure clinics to prevent an admission to hospital or for palliation. It is proposed that in these circumstances that continuing supply of the medicine is available in primary care.

Patients should generally fall into one of the following 3 scenarios:

1. Discharged from hospital on metolazone for short term treatment (≤4 weeks) – **hospital to supply.**
2. Discharged from hospital on metolazone long term – **hospital to supply 2 weeks then GP to prescribe**
3. Initiated at outpatient appointment – **GP to prescribe** initial supply unless there is need to initiate metolazone within 5 days (it may take 5 days before metolazone reaches the patient via a GP prescription because of the time taken to issue a prescription and for community pharmacy to procure the drug). In such cases the consultant should consider issuing a hospital outpatient prescription.

Monitoring
Responsibility for monitoring is shared between the specialist clinicians and the GP.
Monitoring will be co-ordinated with the GP practice.
GPs are responsible for arranging all blood tests.

Monitoring requirements:
Before (i.e. baseline) and during metolazone treatment:

- Urea and electrolytes (U&Es)
- Creatinine
- Blood pressure
- Weight

The interval for monitoring these parameters whilst a patient is on metolazone depends on values for blood pressure, renal function and serum potassium concentration; these indicate likelihood of occurrence of significant adverse effects. Patients at higher risk of adverse events should be monitored more frequently.

Where any one of these parameters is within the range which places the patient at higher risk of adverse effects they should be monitored more frequently - as indicated in the table below.

Risk of patient developing adverse effects:	**Normal risk**	**Increased risk**
Initial monitoring interval (i.e. after initiation or increase in dose)		
SBP (mmHg)	>120mmHg	<120mmHg
Serum potassium concentration	>4.5 mmol/L	<4.5 mmol/L
Monitoring interval	At least every 2 weeks until stable	At least weekly until stable
Monitoring interval once patient is stable on metolazone dose		
SBP (mmHg)	>120mmHg	<120mmHg
Serum potassium concentration	>4.5 mmol/L	<4.5 mmol/L
GFR decline (ml/min)	Decrease equal to or less than 15mL/min	Decrease of more than 15mL/min
Increase in creatinine	<30%	>30%
Monitoring interval	At least every 6months	Every 1 to 3months depending on patient stability

Patients should be weighed or encouraged to self-weigh daily.

- Aim of maintenance therapy is to maintain a constant dry weight, and patients should be advised to contact GP or nephrologist for advice if weight is increasing or decreasing.
- Aim of acute metolazone diuresis is for patient to reach a target dry weight. Patients should be advised to contact GP or nephrologist once target dry weight has been reached for advice.

Action to be taken if abnormal results/adverse effects:
This should be a shared care approach.
The named nephrologist for the patient should be available to offer advice, where necessary, regarding clinical parameters and blood tests. Alternatively, in their absence, the nephrologist of the week can provide advice. For contact details of the nephrologists see the advice and support section below.

The following provides some guidance for GPs if abnormal results are picked up.

Weight Change

- Weight loss beyond target dry weight – consider reducing dose and/or stopping temporarily.
- Weight gain associated with worsening symptoms (increased dyspnoea, fatigue, oedema, weight gain) - confirm compliance and consider increasing dose.

Creatinine levels:

- An increase of less than 30% from baseline does not normally require action. However recheck creatinine within 2 weeks to confirm no further increase.
- If creatinine increases by 30–50% - review volume status and then reduce dose or stop diuretics (if the person is hypovolaemic). Re-measure renal function within 1 week.
- If creatinine increases by more than 50% - assess volume status, check blood pressure and review other renal function tests, including electrolytes and proteinuria. If the person is hypovolaemic, stop the diuretic. If there is any uncertainty, contact nephrologist / heart failure nurses / cardiologist urgently.

Potassium:

- **If potassium level <3 mmol/L (or <4 mmol/L in patients at high risk of cardiac arrhythmias), ensure patient is reviewed urgently to:**
  - **prevent further drop in potassium by initiating potassium supplements.**
  - **assess if admission to hospital is required for urgent potassium replacement.**
- People at high risk of cardiac arrhythmias with even mild hypokalaemia include:
  - Those taking digoxin or drugs that prolong the QT interval (such as amiodarone).
  - Those with paroxysmal arrhythmias, unstable angina, or chronic liver disease.
- Give potassium supplements: Sando K 24mmol TDS for 2-3days, repeat prescriptions until potassium is >4mmol/l. Beware that levels will continue to rise once supplements have been discontinued. Potassium levels should be rechecked on a 24-48hourly basis until >4mmol/L. Then repeat U&Es within 7days.
- **If potassium concentration < 2.5 mmol/L (or 3.5 mmol/L in high-risk people) – admit patient to hospital for urgent potassium replacement.**

Sodium:

- If <131mmol/L repeat level the next day. Consider reduction in diuretic therapy if clinically stable.

Symptomatic Hypotension:(Systolic pressure < 90 mmHg associated with dizziness, fainting, confusion)

- Review antihypertensives, check blood chemistry to exclude other causes for symptoms, consider reduction in diuretic therapy if clinically stable.

Adverse Effects:
Mild gastro-intestinal disturbances, postural hypotension, altered plasma-lipid concentrations, metabolic and electrolyte disturbances including hypokalaemia (see abnormal results section above), hyponatraemia, hypomagnesaemia, hypercalcaemia, hyperglycaemia, hypochloraemic alkalosis, hyperuricaemia, and gout. Less common side-effects include blood disorders such as agranulocytosis, leucopenia, and thrombocytopenia, and impotence. Pancreatitis, intrahepatic cholestasis, cardiac arrhythmias, headache, dizziness, paraesthesia, visual disturbances, and hypersensitivity reactions (including pneumonitis, pulmonary oedema, photosensitivity, and severe skin reactions) have also been reported.

Drug interactions:

- Hypokalaemia caused by thiazides and related diuretics increases cardiac toxicity with cardiac glycosides, flecainide, lidocaine, disopyramide, sotalol.
- Hypokalaemia caused by diuretics increases risk of ventricular arrhythmias with amisulpride, atomoxetine, pimozide (avoid concurrent use with pimozide)
- Hypokalaemia caused by thiazides and related diuretics antagonises action of lidocaine (less likely with topical lidocaine)
- Thiazides and related diuretics reduce excretion of lithium (increased plasma concentration and risk of toxicity)
- Enhanced hypotensive effect when diuretics given with ACE inhibitors, alpha-blockers, angiotensin-II receptor antagonists
- Diuretics increase risk of nephrotoxicity of NSAIDs, also antagonism of diuretic effect
- Please see BNF for further details of interactions

Specialist responsibilities:

1. Confirm diagnosis and indication for metolazone use
2. Discuss benefits and side effects of metolazone treatment with the patient and document that the patient has given informed consent to the unlicensed use of metolazone.
3. Ensure baseline monitoring of biochemical profile & pre-treatment weight of patient completed
4. Ensure that the patient understands and accepts their responsibilities (see section below)
5. Ensure patient is aware of the signs of over diuresis or worsening symptoms, when to seek medical advice from their GP.
6. Arrange for initiation of metolazone as outline above.
7. Provide written instruction to the GP for the initiation and on-going management of metolazone treatment.
8. Ensure patient is aware that GP has to issue a prescription and then it may take 1 or 2 days for community pharmacy to supply as unlicensed.
9. Ensure that a clear management plan is supplied to the GP for the individual patient and that systems exist for GPs to obtain specialist advice and support.
10. Review patient at regular intervals or on GP request to monitor disease progress and continued need for metolazone therapy.
11. Promptly communicate with the GP via a clinic letter any changes in treatment, results of tests undertaken and assessment of adverse events. Clinic letter should clearly state whether the dose has remained the same or if a dose adjustment has been made – specifically highlighting the new dose and for how long treatment should continue.
12. Discontinue metolazone if patient has an adverse event or no longer required diuresis.
13. Report serious adverse events to MHRA on yellow card

GP's responsibilities:

1. Initial referral to secondary care for assessment of CKD.
2. Provide the patient with monthly repeat prescriptions of metolazone at the nephrologist's request as detailed above.
3. Ensure patient is having regular monitoring done as outlined above and ensure results are available on clinical system.
4. Check recent blood results are within range as per above guidance before issuing each repeat prescription of metolazone.
5. Carry out further dose titration according to response or discontinue medication when necessary or requested. Whenever necessary discuss with nephrologist.
6. Ensure practice computer is updated with any dose changes.
7. Seek advice from nephrologist if the patient's condition deteriorates or if there is a change in the patient's status.
8. Contact a nephrologist if not in agreement with the treatment recommendation, or if there is a perceived problem with compliance or concordance, or if they have any questions about the management plan.
9. Report any adverse effects to the nephrologist managing the patient.
14. Report serious adverse events to MHRA on yellow card

Patient's responsibilities:

1. Read the written information provided about the drug from the community pharmacy (Patient Information Leaflet) and have a clear understanding of the risks / benefits of metolazone treatment
2. MUST attend for blood tests.
3. Allow at least 48 hours for the prescription from the GP to be generated (once the GP has agreed to take on the prescribing.)
4. Allow at least 48 hours for the community pharmacy to obtain the metolazone as it is an unlicensed medicine.
5. Report any adverse effects, concerns or lack of understanding of the treatment to the GP or specialist.
6. Weigh themselves regularly as requested by clinicians.
7. Ensure they report signs of over diuresis or any signs of worsening symptoms

Community Pharmacy responsibilities:

1. Ensure prescriber is aware of unlicensed status of medicine
2. Obtain appropriate product *(see section below re metolazone availability).*
3. Supply an English PIL (supplied with product from IDIS)
4. Maintain named patient records as it is an unlicensed medicine

Metolazone availability: It is only available as an unlicensed medicine in the UK.

Please be aware that there are a number of products from different countries with the same brand name Zaroxolyn®. The products differ in strengths and the colourants that are used in them.

The preferred product to be used on Wirral is metolazone (Zaroxolyn®) 2.5mg from Canada as it is the only product that is available as a 2.5mg tablet (the most commonly used strength).

Advice and support:

Principal contact:

Named nephrologist for the patient via the nephrology secretaries.

Contact via switchboard. Telephone: 0151 678 5111 and ask for the secretary of the relevant nephrologist.

Emergency out-of-hours advice only:

Nephrologist of the week, available via the on-call junior renal doctor 7 days a week 9-8pm.

Contact via switchboard. Telephone: 0151 678 5111 and ask for Bleep 0010.

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