

**Shared Care Guideline****Metolazone for Refractory Heart Failure (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.

**Indications:**

Metolazone is approved for use alone or in combination with a loop diuretic by **cardiologists or community heart failure clinics**, as a second line agent for the small number of heart failure patients not responding to first line diuretic treatment.

**In primary care it should only be recommended by the community heart failure clinics to prevent an admission to hospital or for palliation.**

**Dosage and administration:**

Starting dose 2.5mg OD or less frequently, titrating according to response to a maximum of 7.5mg OD

Usual daily dose 2.5mg to 7.5mg

**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; supply may not be immediately available in community pharmacies.

Metolazone can promote dramatic diuresis and disturbance in fluid balance and electrolytes. Patients must be closely monitored and specialist initiation and advice is required.

Treatment with metolazone in the majority of patients will be short term. There may be a 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 4 scenarios:

1. Discharged from hospital on metolazone for short term treatment ( $\leq 2$  weeks) – **hospital to supply**. Hospital to ensure referral to community heart failure team is made and provide advice to GPs regarding monitoring.
2. Discharged from hospital on metolazone long term – **hospital to supply at least 1 week then GP to prescribe**
3. Initiated at outpatient appointment – **hospital to supply at least 7 days** unless metolazone not needed in the next 7 days, in which case GP should initiate supply.
4. Initiated by Community Heart Failure Clinic – **Clinic to supply at least 7 days** if possible; if metolazone not required in the next 7 days GP should initiate supply

**Responsibility for monitoring is shared between the Community Heart Failure Team and the GP.**

**Monitoring will be co-ordinated with the GP practice.**

**Monitoring requirements:**

Before treatment:

- Urea and electrolytes (U&Es) and creatinine

During treatment:

- Urea and electrolytes (U&Es) and creatinine within 7 days of starting treatment and recheck every 7–14 days, depending on the person's stability.
- Patients should be weighed or encouraged to self-weigh daily. Aim for a daily weight loss of 0.5 Kg. If diuresis is extensive, consider earlier testing of renal function.
- Once treatment is stable, measure renal function and serum electrolytes at least once every month

### **Action to be taken if abnormal results/adverse effects:**

This should be a shared care approach. During normal working hours (Monday to Friday, 9am-5pm) the Community Heart Failure Team can be contacted to offer advice regarding clinical parameters and blood tests. GPs are responsible for arranging all blood tests - the following provides guidance for GPs if abnormal results are picked up.

Out of hours and over weekend the GP may be required to make clinical decision based upon results and clinical presentation of patient or the Cardiologist of the week at WUTH can be contacted for advice.

### **Weight Change**

- Daily weight loss in excess of approximately 0.5-1kg – consider reducing dose.

### **Creatinine levels and / or eGFR:**

- If the serum creatinine level increases by more than 20% of baseline or the eGFR decreases by more than 15% of baseline - re-measure renal function within 2 weeks.
- An increase of less than 30% from baseline does not normally require action.
- If creatinine increases by 30–50% (or to greater than 200 micromol/L) or eGFR is less than 30 mL/min/1.73 m<sup>2</sup> - 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% or to greater than 256 micromol/L (eGFR approximately 20–25 mL/min/1.73 m<sup>2</sup>) - 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 heart failure nurses / cardiologist urgently.

### **Potassium:**

- **If potassium level < 3 mmol/L (or 4 mmol/L in high-risk people), ensure patient is reviewed urgently to prevent potassium falling lower and requiring admission to hospital for urgent replacement.** Consider increasing dose of angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB). For patients taking valsartan+sacubitril, dose adjustment of this medication would not be appropriate as valsartan+sacubitril can cause both hyperkalaemia and hypokalaemia.
- Consider adding or increasing spironolactone - discuss with heart failure team if available.
- Potassium supplementation: Sando K 24mmol tds until potassium is >4mmol/l (usually for approximately 3 days and beware that levels will continue to rise once supplements have been discontinued). Potassium levels should be rechecked every 1-2 days until >4mmol/L. Then repeat U&Es within 7days.
- 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.
- **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 next day and contact heart failure nurses for advice as soon as results are available. Consider reduction in diuretic therapy if clinically stable.

**Symptomatic Hypotension** (Systolic pressure < 90 mmHg associated with dizziness, fainting, confusion) - Check blood chemistry to exclude other causes for symptoms, consider reduction in diuretic therapy if clinically stable – discuss with heart failure nurses

**Worsening Symptoms** (increased dyspnoea, fatigue, oedema, weight gain) - contact heart failure nurses to discuss increasing dose.

### **Contraindications:**

- Refractory hypokalaemia
- Hyponatraemia

- Severe renal & hepatic impairment
- Symptomatic hyperuricaemia

**Drug interactions:**

- Hypokalaemia caused by thiazides and related diuretics increases cardiac toxicity with cardiac glycosides (digoxin), 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 ACEI, ARB, valsartan+sacubitril, alpha-blockers
- Diuretics increase risk of nephrotoxicity of NSAIDs, also antagonism of diuretic effect
- Please see BNF for further details of interactions

**Cautions:**

- Close monitoring of U&Es in renal impairment.
- Diabetes and gout may be aggravated
- Hepatic impairment
- Pregnancy

**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, hypochloreaemic 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

**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 and pre-treatment weight of patient
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 and other professionals involved in the patient's care
6. Recommend initiation of metolazone to GP / continue metolazone supply as described in additional information 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 clear backup arrangements exist for GPs for advice and support. GP can contact community heart failure nurses or Consultant of the Week at Arrowe Park Hospital if advice or support is required
10. Review patient at intervals specified below to monitor the patients disease and continued need for metolazone therapy
11. Promptly communicate with the GP via a clinic letter any changes in treatment results of monitoring 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 if patient has adverse event or no longer required diuresis for resistant oedema
13. Report serious adverse events to the Committee on Safety of Medicines (CSM)

<p><b>GP's responsibilities:</b></p> <ol style="list-style-type: none"> <li>1. Initial referral to a Consultant Cardiologist / Community Heart Failure Clinic for assessment of heart failure.</li> <li>2. Provide the patient with repeat prescriptions of metolazone once the specialist has recommended initiation / continuation therapy noting that metolazone is an unlicensed drug and may take longer for community pharmacies to order (see additional information section)</li> <li>3. Ensure patient is having regular monitoring done as outlined on the first page and ensure results are available on clinical system</li> <li>4. Ensure patient has recent blood results within above protocol (appropriate reference ranges) before issuing each repeat prescription of metolazone</li> <li>5. Carry out further dose titration according to response or discontinue medication when necessary or requested. Wherever possible discuss with heart failure nurse</li> <li>6. Ensure practice computer is updated with any dose changes</li> <li>7. Seek advice from the consultant / heart failure nurses if the patient's condition deteriorates or if there is a change in the patient's status</li> <li>8. Contact the consultant if they do not agree 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</li> <li>9. Report any adverse effects to the consultant / heart failure nurses managing the patient</li> <li>10. Report serious adverse events to the Committee on Safety of Medicines (CSM)</li> </ol>	
<p><b>Patient's responsibilities:</b></p> <ol style="list-style-type: none"> <li>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 and unlicensed status</li> <li>2. MUST attend for blood tests</li> <li>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)</li> <li>4. Report any adverse effects, concerns or lack of understanding of the treatment to the GP or specialist.</li> <li>5. Weigh themselves regularly as requested by clinicians</li> <li>6. Ensure they report signs of over diuresis such as a weight loss of more than 0.5mg - 1kg a day, any dizziness, light headedness, fatigue or uraemia or any signs of worsening symptoms</li> </ol>	
<p><b>Community Pharmacy responsibilities:</b></p> <ol style="list-style-type: none"> <li>1. Ensure prescriber is aware of unlicensed status of medicine</li> <li>2. Obtain appropriate product (<i>see section below re metolazone availability</i>)</li> <li>3. Supply an English PIL (supplied with product from IDIS)</li> <li>4. Maintain named patient records as it is an unlicensed medicine</li> </ol>	
<p><b>Secondary Care / Specialist review:</b> Patients have their disease status monitored at a minimum of 6 monthly intervals or if requested to review by the GP. During normal working hours (Monday to Friday, 9am-5pm) the Community Heart Failure Team can be contacted for advice regarding clinical parameters and blood tests</p>	
<p><b>Metolazone availability:</b> 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.</p> <p>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)</p>	
<p><b>Back up advice and support:</b> Heart Failure Specialist Nurses Consultant Cardiologist of the Week at WUTH</p>	<p><b>Telephone:</b> 0151 604 7711 9-5 pm Monday – Friday Via WUTH switch board - 0151 678 5111</p>
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