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Prescribing Advice: Metolazone in Heart Failure

Background

Bendroflumethiazide and metolazone are thiazide/thiazide-like diuretics and are options to use as an adjunctive therapy to loop diuretics in the treatment of resistant oedema in heart failure and chronic kidney disease.

Several years ago, the licensed metolazone product became unavailable and an unlicensed product was imported for use. Recently a new licensed product of metolazone, Xaqua, has become available.

The licence, also known as the marketing authorisation, specifies what conditions the medicine has been approved to treat. The marketing authorisation is an indication that the medicine has been appropriately tested in clinical trials to evaluate its efficacy and safety, and that the dose and method of administration are appropriate.

Now that a licensed metolazone product has become commercially available in the UK, in line with MHRA recommendation, it should be prescribed rather than importing the unlicensed metolazone product even though the licensed product is significantly more expensive than the unlicensed product.

Thiazides/thiazide-like diuretics are particularly useful in patients with cardiorenal syndrome and fluid overload refractory to loop diuretics. In patients with CKD4 (particularly if eGFR<20), the use of thiazide-like diuretics generally requires consensus between the HF and renal teams. Patients under the renal team with CKD4/CKD5 would continue to have their fluid overload medication prescribed by the renal team. Metolazone can be considered in end stage cardiorenal syndrome irrespective of renal function if the patient is for palliative management.

Bioavailability

The manufacturer and the MHRA have deemed Xaqua to have a 2-fold bioavailability compared to other metolazone products. The study to determine this bioavailability was done between Xaqua

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and Metenix (the licensed product which was discontinued in 2012). The currently used unlicensed Zaroxolyn product is deemed equivalent to Metenix and therefore will require the dose of Xaqua to be halved to illicit the same response.

Allergy/Intolerance

- Note that in patients with an allergy to sulfa drugs there can be cross-sensitivity with thiazide-like diuretics.

Advice/Actions

- The decision to add bendroflumethiazide or metolazone to a loop diuretic in patients with loop diuretic-refractory fluid overload is typically taken by a specialist according to local guidelines/recommendation. Careful monitoring of renal function and understanding of sick-day rules to prevent acute kidney injury, hypokalaemia and dehydration is required.

- Due to the 2-fold increase in bioavailability in the licensed product (Xaqua) over the current unlicensed version all patients should be prescribed metolazone by the licensed Xaqua brand name. Xaqua is only available as a 5mg tablet and therefore tablets will need to be halved to provide the appropriate Xaqua dose for many patients. The manufacturers of Xaqua allow for tablets to be divided into equal halves but **quartering of tablets will make the product off-label** and should be discussed at the Heart Failure MDT**.**

- Halving tablets may be difficult for some patients. Strategies to mitigate this may include recommending the use of a tablet cutter or providing tablets already halved (not all community pharmacies will halve tablets). Alternatively, the use of bendroflumethiazide may be considered or amending the frequency and dose of metolazone. This assessment should be made by the specialist team.

- Metolazone (Xaqua) is usually initiated with an initial dose of 2.5mg daily (equivalent to 5mg. This dose can be titrated according to response to a maximum of 5mg (which is equivalent to 10mg of the unlicensed product). Generally, 2.5mg alternate days or twice weekly will suffice when used in combination with a loop diuretic. If Urea>25 consider reducing the dose due to risk of uremic side effects (confusion, itching).

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- Existing patients changing from unlicensed metolazone to licensed metolazone (Xaqua) may have their current dose halved. The clinical response should be monitored carefully, and doses adjusted with close monitoring of the renal function. This may require close liaison between Primary Care and Specialist Teams.
- Patients requiring a dose of metolazone (Xaqua) lower than 2.5mg may be considered for bendroflumethiazide 5mg 1st line, rather than prescribing an off-license dose (1.25mg metolazone (Xaqua)).
- If patients have stable renal function and require ongoing long-term thiazide or thiazide-like diuretics in combination with a loop diuretic, the GP can continue prescribing the diuretic if in the patient's best interests (e.g., ease of access to prescription). The specialist team will advise how frequently the renal function needs to be checked and the patient will remain under their care and have early access if the renal function deteriorates, or the patient becomes more fluid overloaded.
- Patients who are at end of life may not require renal function monitoring. These decisions will be taken at an MDT.

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